TREATMENT OF ILlicit OPIOID AND γ-HYDROXYBUTYRATE OVERDOSE BY HELSINKI EMERGENCY MEDICAL SERVICES

James Boyd

ACADEMIC DISSERTATION

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Dead addicts don’t recover

-Anonymous

For the patients with whom we did not beat the clock
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ABSTRACT

Aims: To examine the characteristics, incidence, treatment and outcome of presumed opioid, γ-hydroxybutyrate (GHB) and γ-butyrolactone (GBL) overdoses involving users of illicit drugs in Helsinki. GHB/GBL were included in this study, despite not being opioids, due to the relative ease with which they can cause potentially fatal respiratory depression. The incidence and time interval of recurrent opioid toxicity after prehospital administration of naloxone, an opioid antagonist, was studied in presumed heroin overdose patients. Naloxone has been reported to have many adverse effects and the effects of naloxone administered during an opioid overdose on the cardiovascular system and catecholamine levels in piglets were studied.

Materials and methods: Patients included in these published retrospective studies were from the following time periods: Study I: 1995-2002, II: 1997-2000, III: 1995-2000, V: 2006-2007. Presumed opioid overdose patients were examined in studies I, II and III. GHB/GBL overdoses among injecting drug users was examined in study V. Recurrent opioid toxicity after prehospital naloxone administration in heroin overdose patients was examined in study III. The effects of naloxone (80 µg/kg i.v.) on the cardiovascular system and catecholamine levels administered during morphine overdose (8mg/kg i.v.) and under propofol anesthesia with spontaneous breathing were studied in eight piglets (IV). In this thesis, previously unpublished data on the incidence of opioid overdose between 2001-2007 and comparison of the characteristics of buprenorphine and heroin overdose patients encountered in 1995-2005 are also included.

Results: Helsinki Emergency Medical Service (EMS) ambulances were dispatched annually to 34,153- 45,118 calls from 1995 to 2007. Of them, 7-8% were coded as intoxications or overdoses. During this time, 436 patients were treated by the EMS for presumed opioid overdose. The peak incidence of opioid overdoses was in the year 2000 (113 cases), after which they declined to 6-26 cases annually. The annual incidence of buprenorphine related overdoses increased from 4 (4% of opioid overdoses) in the year 2000 to 8 (30% of opioid overdoses) in 2007. The annual number of GHB related overdose patients treated by Helsinki EMS increased from 21 to 73 between 2004-2007. There appeared to be a peak in the incidence of both GHB/GBL and opioid related overdoses on Saturdays.

Characteristics of opioid overdose patients
The median age of opioid overdose patients was 28 years (22;33, 25- and 75-percentiles), and 84% were male. Buprenorphine overdose patients had more polydrug, such as alcohol and/or benzodiazepines, use in comparison with heroin overdose patients, 70% versus 33%, respectively. Severe respiratory depression was reported less often with buprenorphine overdoses compared to heroin overdoses, in 67.0% versus 85.4%, respectively.

Outcome of heroin overdose patients with cardiac arrest
Ninety four patients suffered cardiac arrest due to acute drug poisoning/overdose and were thus considered for resuscitation. Resuscitation
was attempted in 72 cases. Cardiac arrest was caused by heroin overdose for 19 patients of which three (16%) were discharged alive. Other agents also induced cardiac arrest in 53 patients, of which six (11%) were discharged alive. The arrest was either EMS witnessed or occurring after the emergency call for all survivors of heroin induced cardiac arrest.

**Characteristics of GHB/GBL overdose patients**
The records of 100 GHB/GBL related overdose patients from 2006-2007 were retrieved. The median age of GHB/GBL overdose patients encountered on weekend nights was 24 years (22;27, 25- and 75-percentiles) and 49% were male. Polydrug use was reported in 62-80% of the cases. Thirty nine patients were encountered on Friday-Saturday or Saturday-Sunday night between 11 pm-6 am. The remaining sixty one patients were outside this time frame. There was a statistically significant difference between these two groups in history of chronic injecting drug use (33% vs. 59%, respectively, p=0.012).

**Recurrent heroin toxicity after prehospital naloxone administration**
Study III included 145 presumed heroin overdose patients. After prehospital care, 84 patients refused further care and were not transported to an Emergency Department (ED). Seventy one (85%) of them were administered naloxone by the EMS. During a 12-h follow up period, none of these patients developed severe recurrent opioid toxicity. The remaining 61 patients were transported to an ED. Prior to transportation, 52 (85%) patients were administered naloxone by the EMS. Fifteen of them were administered naloxone also in the ED and recurrent opioid toxicity was evident either on arrival at the ED or shortly thereafter. Prehospital naloxone was administered either intravenously, intramuscularly (i.m.) or subcutaneously (s.c.). There was a tendency for more frequent recurrent heroin toxicity among the patients with only intravenous administration of prehospital naloxone (13/36) compared with the patients with intramuscular or subcutaneous prehospital naloxone (2/16), p=0.106.

**The effects of naloxone on the cardiovascular system and catecholamine levels in piglets**
The administration of morphine to piglets resulted in an obvious respiratory depression, which was reversed by naloxone. Two severely hypoxemic piglets developed cardiac arrest after naloxone administration. In the other six animals, the administration of naloxone did not provoke arrhythmias, cardiac ischemia or visible evidence of pulmonary edema. There was a statistically significant (p=0.012) increase in norepinephrine levels after morphine administration and before naloxone administration: from 1.9 (1.3-2.3) ng/ml at baseline, to 31.7 (8.3-83.0) ng/ml (median, 25 and 75 percentiles parentheses) after morphine administration. After the administration of naloxone, the catecholamine levels continued to increase in only one of the animals.

**Conclusions:** The incidence of buprenorphine related overdoses increased during the study period, but was still lower in comparison to those involving heroin. Injecting drug users have also started to use GHB/GBL. While recreational drug users use GHB/GBL during weekend nights, a GHB/GBL overdose patient encounter during weekdays has a more probable history of
injecting drug use. Patients with cardiac arrest after heroin overdose have a poor prognosis.

It appears to be safe to leave heroin overdose patients on scene after prehospital treatment with naloxone. Although no statistically significant difference was observed, it seems prudent to administer part of the total naloxone dose s.c. or i.m. to reduce the risk of recurrent respiratory depression. If transported to an ED, an observation period of one to two hours after the last naloxone dose seems adequate. The treating physician must be vigilant, however, due to the high prevalence of polydrug use and high morbidity after non fatal heroin overdose. Furthermore, care should be taken regarding possible chronic disorders and drug rehabilitation should be addressed.

In the experimental animal study, two animals developed cardiac arrest after receiving naloxone while in hypoxemia and bradycardia. Further studies are required to assess the effect of naloxone during opioid-induced hypercapnia and hypoxemia in animals addicted to opioids.
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals I to V.


V. Boyd JJ, Kuisma MJ, Randell TT. γ-hydroxybutyrate and γ-butyrolactone overdoses involving injecting drug users in Helsinki in submission

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ABBREVIATIONS

ALS Advanced life support
BLS Basic life support
cAMP Cyclic adenosine monophosphate
CPR Cardiopulmonary resuscitation
CYP450 Cytochrome P450
ECHO Echocardiogram (cardiac ultrasound)
ED Emergency department
EMCDDA European monitoring centre for drugs and drug addiction
EMS Emergency Medical Services (i.e. ambulance service)
EMT Emergency Medical Technician
FRU First responding unit
GABA Gamma-aminobutyric acid
GBL γ-butyrolactone, gamma-butyrolactone
GCS Glasgow Coma Score
GHB γ-hydroxybutyrate, gamma-hydroxybutyrate
HUCH Helsinki University Central Hospital
I.m. Intramuscularly, intramuscular
I.v. Intravenously, intravenous
I(V)DU Intravenous drug user
MAP Mean arterial pressure (mean systemic blood pressure)
MDMA 3,4-methylenedioxymethamphetamine, ‘ecstasy’
MDPV Methylendioxypyrovalerone
MICU Mobile Intensive Care Unit
MPAP Mean pulmonary arterial pressure
Na-K-ATPase Sodium-Potassium Adenosine Triphosphatase
NRG-1 Naphthylpyrovalerone
OPALS Ontario Prehospital Advanced Life Support
OPC Overall performance category
PaCO2 Partial pressure of carbon dioxide in arterial blood
PaO2 Partial pressure of oxygen in arterial blood
PEA Pulseless electrical activity
ROSC Return of spontaneous circulation
SAMHSA Substance Abuse and Mental Health Services Administration
S.c. Subcutaneously, subcutaneous
UNODC United Nations Office on Drugs and Crime
VF Ventricular fibrillation
Vs. Versus
1,4-BD 1,4-Butanediol
INTRODUCTION

Drug abuse increased rapidly in the latter half of the 1990s in Helsinki and other big cities in Finland. The reasons behind this change have been speculated to be the economic depression, increased unemployment and more liberal opinions towards drug use. Deteriorating drug abuse and crime situations in neighboring countries in combination with the increased freedom of travel of their citizens and lesser border security could also have played a role (Hermanson & Sarvanti 1999). In the greater Helsinki area (Helsinki and the neighboring cities of Espoo and Vantaa) there were estimated to be 4000 to 7400 injecting drug users in 1997. This would have been over 40% more than the estimate made in 1995. Of them, 1000 to 1850 were opioid, including heroin, users (Seppälä et al. 1999). The use of buprenorphine as a drug of abuse increased after 2000 and buprenorphine has surpassed heroin as the most popular opioid among injecting drug users (EMCDDA 2008/country-overview, Vuori et al. 2006). At the beginning of the study period, however, data on non-fatal buprenorphine related overdoses in Finland was scarce.

New drugs of abuse, such as γ-hydroxybutyrate (GHB) and γ-butyrolactone (GBL), also appeared in the late 1990s (Alho et al. 2001). Although not opioids, GHB/GBL related overdoses were also included in this thesis due to the fact that they can cause a potentially fatal overdose easily. The difference between doses causing euphoria versus unconsciousness is narrow (Mason & Kerns 2002, Snead & Gibson 2005), the concentrations of GHB in liquids can vary greatly (Alho et al. 2001) and other central nervous system depressants can increase the effect of GHB/GBL (Alho et al. 2001, Knudsen et al. 2010, Mason & Kerns 2002, Snead & Gibson 2005). GHB/GBL are mainly used as “recreational drugs” by young adults on weekends in nightclubs (Dietze et al. 2008, Snead & Gibson 2005). GHB, however, is considered to be highly addictive (Snead & Gibson 2005), so its wider use is very likely. In addition, GHB/GBL overdoses can be difficult to differentiate from overdoses caused by other substances. During a serious overdose, GHB/GBL can cause respiratory depression, a reduced level of consciousness, miosis and death, similar to opioids (Li et al. 1998 II, Nelson & Olsen 2010, Snead & Gibson 2005). The incidence and pattern of GHB/GBL related overdose involving injecting drug users has not been reported previously.

In conjunction with increasing drug abuse both fatal and non-fatal opioid overdoses increased dramatically in Finland and particularly in Helsinki. In 1995, the Helsinki Emergency Medical Service (EMS) treated nine patients with presumed opioid overdose. Three of them were at the same address, although at different times. Since then, the number of patients doubled each year, until the year 2000 (Unpublished data, Helsinki EMS records). Many of the patients were reluctant to go to a hospital for further care and observation after prehospital treatment. In some other countries, patients with presumed heroin overdose were allowed to sign out and left on scene after prehospital care. Studies on the safety of this strategy were scarce, however. In 1999, the only study available was that by Vilke and others from San Diego, USA (Vilke et al. 1999). The safety of leaving a heroin overdose patient on scene or the
incidence of recurrent opioid toxicity after prehospital naloxone administration has not been studied in Finland before.

In Helsinki, EMS data on cardiac arrests have been collected prospectively since 1994 and survival rates after bystander witnessed ventricular fibrillation (VF) of cardiac causes are excellent (Kuisma & Määttä 1996). The survival after cardiac arrest caused by heroin overdose is poorly documented in the literature, or the results are in discrepancy, as some have reported outstanding survival figures (Bertini et al. 1992, Skulberg et al. 1993) while in some studies there were only few or no survivors (Smith et al. 1992, Sporer et al. 1996). Survival rates after cardiac arrest and resuscitation caused by heroin overdose has not been previously reported in Finland.

Naloxone is an opioid antagonist which is used in the treatment of opioid overdoses (Gutstein & Akil 2001, Nelson & Olsen 2010). Even serious adverse effects, such as seizures, pulmonary edema and cardiac arrest, have been associated to naloxone use in heroin overdose patients (Buajordet et al. 2004, Osterwalder 1996, Yealy et al. 1990). These effects have been postulated to have been caused by increased plasma catecholamine levels (Prough et al. 1984, Smith & Pinnock 1985). Although the adverse cardiovascular effects related to naloxone administration have been reported previously, the mechanism remains unclear.

The aims of the current thesis were first, to examine the characteristics and incidence of opioid overdose among the users of illicit drugs in Helsinki. Also included were the overdoses related to nonmedical use of buprenorphine and survival after heroin overdose leading to cardiac arrest. The second aim was to study the incidence of GHB/GBL overdose involving injecting drug users. The third aim was to study the incidence and time interval of recurrent opioid toxicity after prehospital naloxone administration in heroin overdose patients. This also included examining the safety of allowing heroin overdose patients to sign out after prehospital care. To simulate the effects of naloxone administration to a hypoxic and hypercapnic opioid overdose patient, the cardiovascular effect of naloxone on piglets during opioid overdose was studied.
REVIEW OF LITERATURE

Terminology
Drug abuse, or drug misuse, is the illegal or inappropriate use of drugs. Substance abuse includes solvents, alcohol and illicit drugs such as heroin or cocaine (Brooker 2010). Both drug and substance abuse, however, are used in the literature when referring to the use of illicit drugs. These are drugs that are under international control but are produced, trafficked and / or consumed illicitly (UNODC 2011). Non-medical drug use refers to the inappropriate use of prescription drugs, that usually are controlled under the United Nations (UN) Conventions such as benzodiazepines and opioids (UNODC 2011 II). The term recreational drug use is usually used to describe substance abuse in the context of social interactions, such as parties (Segen 2005).

Poisoning or intoxication refers to exposure to a substance that adversely affects the function of an organ system (Hack & Hoffman 2004), whereas overdose is an intentional exposure to a similar substance. This can be either as a suicide attempt or secondary to drug abuse (Shannon 2007). A serious overdose in this context refers to an overdose that is potentially fatal, usually by causing reduced level of consciousness and/or respiratory depression.

Epidemiology

Drug abuse in general
If one disregards the use of legal substances such as alcohol, tobacco and caffeine, the most commonly used drug remains cannabis. In the USA, less than 20% of youths aged 12 to 17 years reported using cannabis at least once in 2004-2005 (SAMHSA 2005 I). In comparison, over 28% of youths aged 12 to 20 years reported using alcohol in the past month (current use) during the same time period (SAMHSA 2005 II). In Europe, on average 21.8% (71.5 million) of the population aged 15-64 years have tried cannabis at least once, 6.8% (23 million) report using the substance within the last 12 months and 3.8% (12.5 million) within the last 30 days (EMCDDA 2008 I). Also in the EU member states, the lifetime prevalence of the use of amphetamines among adults of the same age group was on average 3.3% and 1.3% had used them within the last 12 months. The respective averages for ecstasy use were 2.8% and 0.8%. Whilst the reported European averages regarding the prevalence of cocaine use were 3.6% having used in their lifetime, 1.2% within 12 months and 0.5% within 30 days, for respondents in the 15-64 years age group (EMCDDA 2008 II).

Problem drug use
Problem drug use is defined as “injecting use, long duration/regular use of substances” and mainly includes the use of opioids, although amphetamines and/or cocaine are also important in some countries. The prevalence of problem drug use is estimated to be 1-10 cases per 1000 population aged 15-64 years in Europe. The prevalence of problem opioid use is estimated to range between one and six cases per 1000 (EMCDDA 2008 III). In some European big cities the prevalence has been higher. In Madrid in 1989, 4-5% of 20-29 year olds reported having used heroin. (Hartnoll 1994).
In 1997, the estimated number of problem drug users in Finland was between 9400 to 14,700, of which 1500-3300 were opioid users (Partanen 2007). In 2005, the estimated number of problem drug users had increased to 14,500-19,000 (Rönkä et al. 2008). In the greater Helsinki area (Helsinki, Vantaa and Espoo) there were estimated to be 5100-8200 problem drug users, 0.9-1.4% of the 15-54-year old age group in 2005. Of them, 1300-2400 used opioids (Partanen et al. 2007). In the other large cities of the European Union (EU), there are estimated to be a similar amount of problem drug users per capita. However, the majority (70-75%) of Finnish problem drug users use amphetamine, while in other EU countries opiates are mainly used (Buajordet et al. 2004, Rönkä et al. 2008, Partanen et al. 2001, Partanen et al. 2004). Injecting drug use is also typical in Finland (Rönkä et al. 2008, Partanen et al. 2004).

In addition to substance abuse, a considerable number of opioid users also suffer from psychiatric disorders. Lifetime rates have been reported to be between 41% and 75% (Cacciola et al. 2001, Partanen et al. 2004, Rodriguez-Llera et al. 2006). Among regular heroin users aged 18-30 years in Barcelona, Spain, over two thirds have a dual diagnosis (Rodriguez-Llera et al. 2006). Also, among drug injectors the prevalence of bloodborne diseases, mainly hepatitis B and C, remains high. Hepatitis B core antigen antibodies were found in over 40% of injecting drug users for a majority of countries in the EU, whilst over 15-90% carried detectable hepatitis C antibody (EMCDDA 2008 IV). The HIV epidemic among intravenous drug users seems to have stabilized or to be declining in the EU countries. This follows a peak of new infections in 2001-2002 due to outbreaks in Estonia, Latvia and Lithuania (Hamers & Downs 2003, EMCDDA 2008 IV). The highest incidences of new infections remain in Estonia, Latvia and Portugal with 142.0, 47.1 and 66.5 cases per million population, respectively, in 2006 (EMCDDA 2008 IV). The incidence of HIV infections among Finnish injecting drug users peaked in 1999 (n=98 in the Helsinki area), after which it has declined, probably due to active outreach programs and the availability of clean needles and syringes (Kivelä et al. 2007). In comparison, the incidence of new HIV cases related to injecting drug use in Russia and Ukraine in 2006 was high and increasing with 78.6 and 152.9 new cases per million population, respectively (EMCDDA 2008 IV).

**Characteristics of GHB use**

GHB and its precursors have been used as drugs of abuse in the USA since the 1980’s and in Europe since the 1990’s (Drasbek et al. 2006). According to a study done in Australia, 1.8% of 20-29 year olds had used GHB at least once (Degerhardt & Dunn 2007). During the new millennium, GHB related emergencies seem to have increased in Europe (EMCDDA 2008 V), especially in relation to opiate overdoses (Miro et al. 2002). In comparison, in a study done in the United States poison control centers, GHB related calls decreased from 1999 to 2003. It is unclear whether this was due to a true decrease, a decrease in seeking help, or a decrease in reporting GHB related emergencies (Anderson et al. 2006).

GHB and its precursors have been profiled as “party drugs” used mainly in night clubs, during dance parties (raves) and the likes (Dietze et al. 2008,
Snead & Gibson 2005, West et al. 2008). They have also been used by bodybuilders in the belief that they boost growth hormone production, and gained notoriety as a “date rape” drug (Snead & Gibson 2005). GHB/GBL related emergencies do occur more often during weekend nights (Miro et al. 2002, Wood et al. 2008). Polysubstance (alcohol, other sedatives, 3,4-methylenedioxymetamphetamine (MDMA) and cocaine being the most typical) use is a common finding in GHB/GBL overdose patients (Li et al. 1998 I, Miro et al. 2002, Snead & Gibson 2005, West et al. 2008, Wood et al. 2008). There is evidence that so called club drug, including GHB/GBL, use has moved beyond rave culture into mainstream among other more traditional drugs of abuse (Hopfer et al. 2006).

Non-fatal opioid overdoses
According to ambulance service records, the incidence of non-fatal opioid overdoses treated with naloxone by EMS varies from 7.24 to 23.8 events/10,000 persons/year (Buajordet et al. 2004, Degenhardt et al. 2001, Sporer et al. 1996). In a study done in Vienna, Austria, the municipal ambulance service treated 707 patients involved in 1087 opioid related emergencies from 1.6.1994 to 31.8.1995. Naloxone was administered to 632 patients. Non-fatal opioid-use related emergencies were on average 6.8 times as prevalent as fatal opioid overdoses. Also in the same study, 189 (27%) patients were involved in 52% of the non-fatal overdoses (Seidler et al. 2000). In Oslo, a city with the same population size as Helsinki (ca. 500,000) and a similar estimate of injecting drug users (ca. 6000), the emergency medical services treated 1192 suspected acute opioid overdoses from 1.2.1998 to 31.1.1999 (Buajordet et al. 2004).

While most overdoses occur in the presence of other people (Darke & Hall 2003, Powis et al. 1999, Tobin et al. 2005), opioid abusers seek medical attention reluctantly during an overdose. The initial responses of the witnesses are often either delayed or inappropriate (Darke et al. 1996, Darke & Hall 2003, Tobin et al. 2005). An ambulance is called for only half of the occasions: calling an ambulance is the first action taken in 17-39% of the incidents. Several individual and social factors that influence calling an emergency dispatching centre have been identified; the fear of police involvement is the single most important reason not to call professional help (Darke et al. 1996, Tobin et al. 2005)

In different studies, 23-68% of heroin users report having experienced an overdose at least once and 29-41% of them had at least one in the preceding 12 months (Darke et al. 1996 I, Gossop et al. 1996). The mean number of overdoses was 3.6 (2.6 to 4.6; range 1-34) (Gossop et al. 1996). The prevalence of overdose increases with the length of heroin-using career: 54% of users overdose in their first five years of use, whilst 78% of users have overdosed in their first ten years of use. Fewer than 25% of the patients had experienced their first overdose within the first year of heroin use (Darke et al. 1996 I). The reported incidence of concomitant use of other CNS depressants in non-fatal overdoses varies from under ten (Bertini et al. 1992) to ninety percent (Cook et al. 1998). In a study by Pedersen et al., blood samples were drawn from presumed opioid overdose patients treated by EMS. Out of 52 patients, 45 had positive blood samples for heroin and 41 (79%) had concomitantly used other
drugs (minor tranquilizers, alcohol, amphetamine, cocaine and/or carbamazepine) (Pedersen et al. 1997).

Fatal opioid overdoses
Mortality among drug users is 6-20 times higher than that of peers of the same age and sex in the general population (Darke & Zador 1996, Gossop et al. 2002). Overdose is the main cause of death among opioid users in many countries (EMCDDA 2008 IV, Gossop et al. 2002, Webb et al. 2003). The number of fatal poisonings of drug users increased in all the Nordic countries from 1991 to 1997. The death rate per 100,000 inhabitants increased from 1.16 (n=36) to 1.83 (n=52) in Finland, while the death rates in Denmark and Norway were four times higher. Finland differed from the other Nordic countries in having the highest death rate in the age group of 20-24 years. The highest death rate was in Norway in the age group 30-34 years and in Denmark and Sweden in the age group 35-39 years. Heroin/morphine was found to be the single most important cause of death, varying from 38% in Finland to 93% in Norway (Steentoft et al. 2001). Fatal overdoses continued to increase from 1997 to 2002, except for Denmark. The highest death rate continued to be in Norway (8.44, n=232), while Finland and its neighboring country Sweden had death rates of 2.93 (n=94) and 2.56 (n=136), respectively. In Finland, the maximum death rate continued to be in a younger age group in comparison to Norway and Denmark. Buprenorphine was the main intoxicant in 17%, amphetamines in 12-14% and heroin/morphine in 10% of fatal overdoses among Finnish drug users in 2002. In other Nordic countries only one buprenorphine death was encountered, while heroin/morphine continued to be the single most important cause of death (72% in Norway) (Steentoft et al. 2006).

Death is most likely caused by respiratory depression and hypoxemia during opioid overdose (Gutstein & Akil 2001). In many victims of fatal overdoses, however, morphine levels in the blood were found to be lower, or similar to levels found in non-fatal overdose patients or patients that have died of other causes. This could be caused by loss of tolerance, the concomitant use of other central nervous system (CNS) depressants, chronic or acute illness or genetic predisposition (Warner-Smith M et al. 2001, White & Irvine 1999) (Table 1). Tolerance might also develop at a different rate for the respiratory depressant versus the euphoric effects of opioids. Thus, the difference between a lethal and an intoxicating dose of heroin is decreased in experienced users (White & Irvine 1999). In the autopsies of fatal heroin overdose victims, alcohol and benzodiazepines have often been detected (Darke & Zador 1996). Studies of fatal overdose cases in Finland in 1997 and 2002 showed that benzodiazepines were detected in 67% (1997) and 70% (2002) of patients, whilst alcohol was detected in 44% (1997) and 47% (2002) (Steentoft et al. 2001, Steentoft et al. 2006). Systemic factors such as hepatic dysfunction due to hepatitis and impaired pulmonary function caused by tobacco smoking or pulmonary infections might play a role in fatal overdoses. Injecting drug users have a high prevalence of hepatitis and tobacco smoking (both up to 90%). Malnutrition and poor hygiene predispose them to infections (including respiratory). Recurrent non-fatal overdoses with pulmonary edema or aspiration pneumonia may cause cumulative impairment of pulmonary function contributing eventually to a fatal overdose (Warner-Smith M et al. 2001). The
role of impurities or adulterants in current opioid overdose deaths is considered to be marginal (Darke & Zador 1996).

*Heroin and pulmonary edema*

Pulmonary congestion and edema related to opioid use were first described in 1880, before widespread heroin use (Loria et al. 1967). Several factors have been implicated, but the mechanisms behind the condition still remains unclear (Loria et al. 1967, Reed & Glauser 1991). It has been reported to occur after intravenous, intranasal or oral administration of any narcotics (Benowitz et al. 1979). Signs and symptoms consist of tachypnea, tachycardia, hypoxemia and bilateral alveolar infiltrates on chest roentgenogram (Morrison et al. 1970, Reed & Glauser 1991). Unilateral or even localized radiographic findings have been also reported, however (Sporer & Dorn 2001). The onset of symptoms are usually immediate or within 1-2 hours, but may appear later after the administration of an opioid antagonist. After methadone use, symptoms have appeared with a six hour delay (Benowitz et al. 1979). Cessation of radiological findings and alleviation of hypoxemia in uncomplicated cases occur within 24-48 hours (Morrison et al. 1970, Sporer & Dorn 2001). The incidence of noncardiogenic pulmonary edema related to heroin overdose has declined in the last decades (Sporer & Dorn 2001). In studies from 1964 to 1970, 48% to 75% of the heroin overdose patients admitted to hospital had pulmonary edema (Duberstein & Kaufman 1971, Morrison et al. 1970). In six more recent studies from 1992 to 2001, the incidence of pulmonary edema in opioid overdose patients brought to the ED has been from 0.8% to 2.4% (Bertini et al. 1992, Osterwalder 1995, Smith et al. 1992, Sporer et al. 1996, Sporer & Dorn 2001). Exceptionally, the incidence was reported to be as high as 10.4% in a recent study (Sterrett et al. 2003).

**Table 1:** Risk factors of heroin overdose (both fatal and non-fatal).

| Male sex | 1,4,7,8,9,10 |
| Age: late 20s and early 30s | 1,4,8,9,10 |
| Single | 1,10 |
| Unemployed | 1,10 |
| Homelessness | 11 |
| Anxiety | 21 |
| History of heroin dependence | 1,4,9 |
| Not being in treatment for dependence | 1,4 |
| Intravenous use of heroin | 1,2 |
| Concomitant use of alcohol and/or benzodiazepines | 1-6, 8-11 |
| Recent release from incarceration | 1 |
| Sporadic use | 2 |
| Long term HIV+ | 2 |
| Higher than usual dose | 3 |
| Heroin stronger than usual | 3,7 |
| Using heroin again after abstinence | 3 |
| Deliberate self-harm | 3 |
| Weekends | 4,5 |
| Genetic factors | 12 |


*moderate association of average heroin purity and the range of heroin purity to overdose fatalities.

Pharmacology

Opium, the dried extract of the poppy plant (*Papaver somniferum*), has been used by man at least since the third century B.C. Morphine, codeine and papaverine were isolated from opium in the early half of the 19th century (Gutstein & Akil 2001). Heroin was first synthesized from opium in 1874 and was originally marketed and used as cough medicine since 1898. The first references to heroin addiction were published in 1912 in the USA, where its use was banned from medical use in 1924. Many countries followed suit, with the exception of the UK (Sneader 1998). The term *opiate* refers to alkaloids derived directly from opium, whereas *opioids* refer to all substances that are able to produce opium like effects by binding to opioid receptors. Opioids include naturally occurring peptides such as endorphins, semi synthetic (heroin, oxycodone, buprenorphine) and synthetic opioids (fentanyl, methadone, and meperidine) (Gutstein & Akil 2001, Nelson & Olsen 2010).

Opioid receptors are present both in the central nervous system and on peripheral nerves. Four major classes of receptors have been identified (µ, δ, κ and nociceptin/orphanin). In addition to these, several subtypes have been proposed (Gutstein & Akil 2001). All opioid receptors are coupled to G proteins. Upon activation of the receptor, G proteins reduce the amount of cyclic adenosine monophosphate (cAMP), close calcium (Ca²⁺) channels, or open potassium (K⁺) ion channels (Nelson & Olsen 2010). The majority of clinically used opioids exert their effects via µ₁ and µ₂ receptors (Gutstein & Akil 2001). The clinical effects of these receptors include euphoria, physical dependence, sedation and respiratory depression in addition to supraspinal and spinal analgesia (Nelson & Olsen 2010).

The classical signs of opioid intoxication, known as the opioid toxidrome, consist of depressed mental status, hypoventilation and miosis (Nelson & Olsen 2010). Opioids reduce the sensitivity of central receptors to hypercapnia and hypoxia (Weil et al. 1975). Miosis is caused by stimulation of parasym pathetic neurons in the Edinger-Westphal nucleus (Lee & Wang 1975). In addition, mild hypotension might occur, but bradycardia is unusual. Seizures are also unusual, unless meperidine, propoxyphene or tramadol are used (Nelson & Olsen 2010).
**Heroin and morphine**

Heroin or 3, 6-diacetylmorphine, can be synthesized by acetylation of morphine. It has been used as highly water soluble hydrochloride salt or more commonly today, as a very poorly water soluble base. When injected, heroin base is heated and mixed with an acid, typically citric acid (Newton-John et al. 1984). Heroin base can also be smoked by heating it on an aluminum foil and inhaling the vapor ("Chasing the dragon") and by intranasal administration ("snorting"). Street-level heroin often contains adulterants in an attempt to increase profits. Substances such as caffeine, barbiturates, quinine, strychnine, acetaminophen, methaqualone, thallium, lead, cocaine, amphetamines, chloroquine and scopolamine have been reported as an adulterant. Liberal use of quinine as an adulterant has even been suggested to have caused excessive deaths of heroin users in the late 1970s and early 1980s in the US (Nelson & Olsen 2010).

Heroin is a prodrug, whose pharmacological effects are caused largely by its metabolites 6-acetylmorphine, morphine and morphone-6-glucuronide (Inturrisi et al. 1984). Heroin contains two acetyl ester groups in the 3- and 6-hydroxyl position of morphine. These groups enhance its ability to penetrate through the blood-brain barrier (Oldendorf et al. 1972). Exhibiting little opioid receptor affinity itself, heroin is rapidly hydrolyzed by serum and liver esterases to 6- acetylmorphine and morphine. Morphone is further conjugated to glucuronides to form morphone-3-glucuronide and morphone-6-glucuronide by enzymes in liver, kidney and brain. Finally, the metabolites of morphone are excreted mainly into urine and, to a lesser extent, into bile (Inturrisi et al. 1984, Rook et al. 2006 I).

After intravenous (i.v.) administration, heroin levels in the serum peak in less than one minute, after which they rapidly decline (Inturrisi et al. 1984). The terminal half-life of heroin has been reported to be 2-7.6 minutes (Inturrisi et al. 1984, Rentsch et al. 2001, Rook et al. 2006 II). Heroin cannot be detected 45 minutes after intravenous bolus injection. Both morphone-6-glucuronide and morphone are immediately formed after intravenous injection of heroin and peak concentrations are measured in 2 minutes and 2-45 minutes (mean 7.8 minutes), respectively. The peak concentrations of morphone-3-glucuronide and morphone-6-glucuronide are reached in one hour after injection of heroin (Rook et al. I). The half-life of morphone-3-glucuronide is 1.8-4.3 hours, whilst that of morphone-6-glucuronide is 1.7-2.4 hours (Girardin et al. 2003).

**Pharmacological interactions of heroin**

Alcohol and benzodiazepines potentially increase the effects of heroin via pharmacodynamic interaction (White & Irvine 1999). Pharmacokinetic interactions may also exist. According to data from studies on pharmacokinetic interactions of cocaine and heroin (Kamendulis et al. 1996) and post-mortem studies on drug overdose victims (Polettini et al. 1999, Polettini et al. 2005), alcohol and cocaine may inhibit morphone metabolism. *In vitro* benzodiazepines also inhibit morphone metabolism (Wahlstrom et al. 1988), but this has not been demonstrated *in vivo* (Rook et al. 2006 II).
**Buprenorphine**

Buprenorphine is a morphine derivative with partial \( \mu \)-opioid receptor agonist and \( \kappa \)-opioid receptor antagonist properties. It has a strong affinity to opiate receptors and thus a long lasting duration of action. It has been used for both postoperative analgesia and chronic pain management. Buprenorphine has similar side effects to other opiates, including respiratory depression, sedation and miosis (Walsh et al. 1994). Depending on dosage, peak plasma concentrations are reached within 30 to 60 minutes of sublingual administration (Walsh et al. 1994). Buprenorphine rapidly crosses the blood-brain barrier (Marquet 2002). After an intravenous injection of 1.2 mg, buprenorphine’s elimination half-life ranged from 97 minutes to over 8 hours (Kuhlman et al. 1996). Buprenorphine is mainly metabolized in the intestinal wall and by the liver. CYP450 3A4 catalyzes its dealkylation to norbuprenorphine (Marquet 2002). After intravenous injection norbuprenorphine appears in the plasma immediately and average peak plasma concentration is reached in about 10 minutes. After glucuroconjugation, 90% of the dose is excreted into bile, and to a lesser extent, into urine (Kuhlman et al. 1996, Marquet 2002).

Being an opioid agonist and antagonist, buprenorphine has a ceiling effect with high doses; the side effects increase only to a certain point as the dosage is increased. This does not, however, seem to apply to its analgesic effects (Dahan et al. 2006). After increasing the dosage, the antagonistic effect of buprenorphine increases. In rats, doses from 3 to 90 mg/kg have no significant effects on arterial blood gases (Gueye et al. 2001). Respiration should be maximally suppressed at a sublingual dose of 16 mg in non-opioid dependant humans (Walsh et al. 1994). In the absence of other drugs and when the proper drug form is used (that is intended for intravenous use), intravenous buprenorphine also appears to have a high safety margin. After intravenous administration, the greatest mean decrease in oxygen saturation was obtained with a dose of 8 mg. The respiratory depressant effect caused by buprenorphine is also short lived and mild (Umbricht et al. 2004).

There seems to be an increased risk of respiratory depression with the concomitant use of buprenorphine and benzodiazepines even at therapeutic doses (Forrest 1983, Papworth 1983). In rats, high doses of midazolam or buprenorphine alone had only limited effects on respiration. When administered together in similar doses, they acted synergistically (Gueye et al. 2002 II). Doxapram boluses and infusion have been used to increase respiratory rate (Sekar & Mimpriss 1987), whilst naloxone, an opiate receptor antagonist, produces only partial reversal even when high doses are used (Heel et al. 1979). Instead, it has been used to increase analgesia after the use of buprenorphine (Schmidt et al. 1985).

Buprenorphine seems to be as effective as methadone and levomethyl acetate in maintenance therapy for opiate dependent patients. It is available both alone and in combination with naloxone. Daily or three-weekly administrations have been used (Johnson et al. 2000, Mendelson et al. 1996, O’Connor & Fiellin 2000). Subutex® (a buprenorphine formulation available in 0.4, 2 and 8 mg tablets for sublingual use) has been available in France
since 1996. By the year 2001 there were approximately 60,000 drug addicts on Subutex® maintenance (Kintz 2001).

Buprenorphine is used as a drug of abuse in several countries, especially France and New Zealand (Basu et al. 2000, Hammersley et al. 1995, Kintz 2001, San et al. 1993, Sporer 2004). In a study done in Marseille, France, 58% of i.v.-drug users recruited at pharmacies and needle exchange programs reported injecting buprenorphine (Subutex®) at least once in the previous 6 months. The majority also injected heroin and/or cocaine, but 24% of the total sampled reportedly injected only buprenorphine (Obadia et al. 2001). In 1998 a series of 20 fatalities in France involving buprenorphine was reported. For 19 patients there was concomitant use of psychotropics. In all but one of the cases benzodiazepines were present (Tracqui et al. 1998). In 2001 an epidemiological study of a further 117 fatal cases was published. Again there was concomitant intake of psychotropics in all but one of the cases. Most often benzodiazepines were involved, however other drugs included neuroleptics, tricyclic antidepressants and serotonin uptake inhibitors. Other opiates (morphine, codeine, methadone, pethidine and propoxyphene) were involved in 23 cases: ethanol was involved in four cases. Another risk factor for a potentially fatal overdose is the use of high dosage tablets i.v. or as massive oral doses (Kintz 2001, Tracqui et al. 1998). An overdose leading to death by the oral intake of a massive dose of buprenorphine and benzodiazepines has also been described (Gaulier et al. 2000).

Naloxone

Naloxone is a synthetic N-allyl derivative of oxymorphine and acts by competitively binding to opioid receptors (mainly μ-receptor) (Gutstein & Akil 2001, Handal et al. 1983). Naloxone readily reverses respiratory depression and coma caused by exogenous opioids (Nelson & Olsen 2010): it is highly lipid soluble and rapidly distributed throughout the body after intravenous administration. Initially high central nervous system levels are short-lived due to rapid redistribution (Ngai et al. 1976). Effects can be seen in 1-2 minutes after i.v. injection and within 15 minutes after intramuscular (i.m.) or subcutaneous (s.c.) injection (Handal et al. 1983). Five minutes after i.v. bolus injection, 90-97% of the administered dose is no longer found in the serum. The terminal half-life of naloxone is 47-64 minutes (Aitkenhead et al. 1984, Glass et al. 1994, Ngai et al. 1976). Naloxone has previously been used to reverse ethanol induced depression of hypoxic and hypercapnic drive (McCaulley et al. 1988, Michiels et al. 1983), and to manage overdoses caused by ethanol and other central nervous system depressants (Howland & Nelson 2010, Mackenzie 1979, Sorensen & Mattison 1978).

Adverse effects related to naloxone administration are presented in Table 2. In 0.4-1.1% the adverse effects were serious, such as arrhythmias, hypertension, convulsions, pulmonary edema and cardiac arrests. These have been reported in spontaneously breathing patients postoperatively (Andree 1980, Azar &
Table 2: Adverse events reported after naloxone use.

<table>
<thead>
<tr>
<th>Event</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressiveness</td>
<td>1-3</td>
</tr>
<tr>
<td>Arrhythmias (other than tachycardia)</td>
<td>4-6</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>2, 7, 8</td>
</tr>
<tr>
<td>Confusion</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4, 9-11</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1, 9, 12</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>2, 13-17</td>
</tr>
<tr>
<td>Shivering</td>
<td>1</td>
</tr>
<tr>
<td>Seizures</td>
<td>1, 2, 9, 18</td>
</tr>
<tr>
<td>Sweating</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
</tr>
<tr>
<td>Tremor</td>
<td>1</td>
</tr>
</tbody>
</table>

2. Osterwalder 1996.

Turndorf 1979, Partridge & Ward 1986, Prough et al. 1984, Wride et al. 1989), in intubated patients after cardiac surgery (Michaelis et al. 1974) and in heroin overdose patients (Buajordet et al. 2004, Osterwalder 1996, Yealy et al. 1990). The naloxone dose used in these studies varied from 0.08 to 2.8 mg.

A sudden surge of catecholamines which then cause cardiac arrhythmias and neurogenic pulmonary edema is one of the proposed mechanisms of the cardiopulmonary side-effects related to naloxone administration (Prough et al. 1984, Smith & Pinnock 1985). After naloxone administration, increases in plasma catecholamine levels were seen in anaesthetized and opioid-addicted humans undergoing acute detoxification (Kienbaum et al. 2000), conscious and opioid-naïve humans (Manneli et al. 1984), conscious and unrestrained morphine-dependent rats (Chang & Dixion 1990), and opioid-naïve dogs (Mills et al. 1988). In dogs, hypercapnia augmented the increase of catecholamine levels (Mills et al. 1988).

When naloxone was used to antagonize exogenous opioids, increases in heart rate, cardiac output and systemic blood pressure were seen in humans.
(Desmonts et al. 1978, Kienbaum et al. 2000), dogs (Patschke et al. 1977, Schweichel et al. 1979) and pigs (Strom et al. 1985) both during (Kienbaum et al. 2000, Patschke et al. 1977, Schweichel et al. 1979, Strom et al. 1985) and after anesthesia (Desmonts et al. 1978). In vitro naloxone has been demonstrated to have a depressant effect on the myocardium (Kim et al. 2004). On the other hand, during normoventilation and without the presence of opioids, naloxone administered even in high doses had no effect on the cardiovascular system of anaesthetized dogs (Freye 1974, Schweichel et al. 1979) or neither anaesthetized nor conscious humans (Estilo & Cottrell 1982, Manneli et al. 1984).

Naloxone administered in the prehospital setting by paramedics has generally been considered to be safe with few severe adverse effects related to its use (Buajordet et al. 2004, Yealy et al. 1990). The role of naloxone in these events is unclear and some events are probably a result of sudden opioid withdrawal or hypoxemia caused by the overdose (Buajordet et al. 2004). In general, the naloxone doses used in the prehospital setting vary from 0.4-6 mg (Bertini et al. 1992, Buajordet et al. 2004, Seidler et al. 2000, Sporer et al. 1996, Vilke et al. 2003, Wanger et al. 1998, Yealy et al. 1990). Naloxone is generally administered i.v. by paramedics, but intramuscular (Sporer et al. 1996, Vilke et al. 2003) and subcutaneous (Wanger et al. 1998) routes have also been used to good effect. Intralingual (Maio et al. 1987), submental (Salvucci et al. 1995) and endotracheal (Tandberg & Abercrombie 1982) administration have been used in emergency situations when an intravenous route was not available. Intranasal naloxone administration is a novel method that has also been used by paramedics in the prehospital setting (Barton et al. 2002).

**Gamma-hydroxybutyrate, GHB**

GHB, a short-chained fatty acid, is found in the mammalian brain and is both a precursor and a product of GABA (gamma-aminobutyric acid) metabolism (Snead & Gibson 2005). GHB was synthesized in 1964 and used briefly as a general anesthetic agent in the 1960-70s. However, due to its unpredictable duration of action, lack of analgesic effect and adverse effects, such as nausea, vomiting and abnormal electroencephalographic (EEG) findings, it subsequently fell out of favor (Drasbek et al. 2006, Mason & Kerns 2002). GHB has since found limited clinical use in the treatment of narcolepsy, alcoholism and opiate addiction (Li et al. 1998 II, Snead & Gibson 2005).

GHB precursors used as drugs of abuse, such as GBL and 1,4-butanediol, are metabolized to GHB *in vivo*. GHB’s effects are mainly mediated via GABAb-receptor, but a specific GHB-receptor also exists. GHB has also effect on the dopaminergic, serotonergic, acetylcholinergic and endogenic opiate systems (Drasbek et al. 2006, Snead & Gibson 2005).

GHB doses of 20-30 mg/kg cause euphoria and drowsiness (Snead & Gibson 2005), while doses of 50-70 mg/kg cause coma in adults (Mason & Kerns 2002). The concentration of GHB in liquids has been reported to vary from 75 to 500 mg/ml (Alho et al. 2001). After oral intake, the onset of GHB’s effect begins in approximately 15 minutes (Li et al. 1998 II). Peak plasma levels are reached within 40 minutes and its half-life in plasma is 20-30 minutes. Ethanol and GHB’s precursor, 1,4-butanediol, share a common metabolic
pathway (both are metabolized by alcohol dehydrogenase) (Snead & Gibson 2005). Retroviral drugs can also decrease GHB metabolism via inhibition of the cytochrome P450 (CYP450) system (Mason & Kerns 2002). GHB can be detected in urine for up to 12 hours after dosing (Snead & Gibson 2005). Patients typically recover within two to six hours (Mason & Kerns 2002).

The clinical effects of GHB include euphoria, ataxia, nystagmus, hypnosis, amnesia, somnolence and vomiting. In an overdose GHB acts mainly as a central nervous system depressant causing reduced level of consciousness, respiratory depression, myoclonus and bradycardia (Li et al. 1998 II, Snead & Gibson 2005). In a study on GHB-associated deaths, blood toxicology was negative for co-intoxicants in 34% of the victims of drug-caused deaths (Zvosec et al. 2011). Other central nervous system depressants, such as opioids, can also increase the toxicity of GHB (Alho et al. 2001, Knudsen et al. 2010, Mason & Kerns 2002, Snead & Gibson 2005). In some cases, agitation and aggressive behavior is present, sometimes interspersed with periods of sedation and respiratory depression (Li et al. 1998 I, Zvosec & Smith 2005); GHB has also been showed to increase sympathetic activity at least in animal models (Hicks et al. 2004).

GHB use can lead to addiction. Cessation of long lasting and continuous GHB use can lead to withdrawal symptoms similar to those after benzodiazepine use. In these cases, GHB has been used several times a day, usually every 1-3 hours or at least every 8 hours. Withdrawal symptoms may start within 1-6 hours of cessation of drug use. The symptoms and signs can include restlessness, agitation, autonomic nervous system instability, convulsions, rhabdomyolysis and sometimes fatal pulmonary edema (Snead & Gibson 2005).

**Prehospital emergency medical services and opioid overdoses**

Prehospital care provided by EMS has been shown to potentially reduce overdose mortality (Bertini et al. 1992, Paredes et al. 2004). When comparing Florence (physician staffed Mobile Intensive Care Unit-MICU) to other big Italian cities without EMS, a reduction in drug-related mortality was seen. Heroin was involved in all but three of the 431 drug-related deaths in these cities during the study period (Bertini et al. 1992). EMS ambulance records can also provide useful information on non-fatal opioid overdoses, such as incidence, location, circadian periodicity, age, gender and polydrug use (Alexander et al. 2004, Bammer et al. 1995, Degenhardt et al. 2001, Seidler et al. 2000).

**Prehospital care and disposition after prehospital care**

In the prehospital setting, opioid overdose patients are treated with bag-mask ventilation and naloxone in many EMS systems (Bertini et al. 1992, Buajordet et al. 2004, Seidler et al. 2000, Sporer et al. 1996, Vilke et al. 2003, Wanger et al. 1998, Yealy et al. 1990). Several emergency medical services appear to allow heroin overdose patients to sign out after prehospital treatment (Buajordet et al. 2004, Seidler et al. 2000, Sporer et al. 1996, Vilke et al. 2003), yet the only previously published studies on the mortality of these patients is by Vilke et al. In published studies, the most patients are allowed to
sign out in Norway (85%) (Buajordet et al. 2004) and the least in the USA (12%) (Vilke et al. 2003).

**Opioid (heroin) overdoses – how long should these patients be monitored?**
The most feared immediate complications of an opioid overdose are recurrent opioid toxicity and respiratory depression (Nelson & Olsen 2010, Watson et al. 1998), in addition to non-cardiogenic pulmonary edema (Osterwalder 1995, Smith et al. 1992, Sporer et al. 1996, Sporer & Dorn 2001). The reappearance of respiratory depression after reversing opioid toxicity with naloxone depends on several factors related to naloxone (Chamberlain & Klein 1994, Handal et al. 1983), the opioid used (Chamberlain & Klein 1994, Watson et al. 1998,) and other variables, such as individual metabolic rate (Chamberlain & Klein 1994, Handal et al. 1983). The incidence of noncardiogenic pulmonary edema related to heroin overdose has declined in the last decades (Sporer & Dorn 2001): in recent studies, the incidence of pulmonary edema in opioid overdose patients brought to the ED has been from 1% to 2.4%. Most of the cases have showed signs of respiratory insufficiency within one hour of arrival at the ED (Osterwalder 1995, Smith et al. 1992, Sporer et al. 1996), except for one patient that was found dead 8 hours after leaving the ED (Osterwalder 1995). The recommended times of observation for patients with presumed opioid overdose vary greatly in the literature (Nelson & Olsen 2010, Osterwalder 1995, Smith et al. 1992, Sporer 1999). Other opioid antagonists, such as naltrexone and nalmefene, are usually longer-acting than naloxone (Gutstein & Akil 2001). They are, however, not recommended in the management of acute opioid overdoses of opioid abusers due to the fear of prolonged withdrawal syndromes (Howland & Nelson 2010). It has been also postulated that a discharged patient might try to overcome antagonism by self-administering higher doses of opioids (Howland & Nelson 2010).

**Poisoning or opioid overdose leading to cardiac arrest and resuscitation**
In young adults, the most common reasons for unexpected cardiac arrest are of cardiac origin, such as ischemic heart disease, myocarditis and hypertrophic obstructive cardiomyopathy (Amital et al. 2004, Safranek et al. 1992). In patients considered for resuscitation in Helsinki in 1994-1995, the most common non-cardiac causes of out-of-hospital cardiac arrest were non-traumatic bleeding (n=34), intoxication (n=27), near-drowning (n=21), pulmonary embolism (n=17), trauma (n=15), intracranial processes (n=14), choking (n=13), pneumonia (n=11), asthma (n=8), hanging (n=8), malignancy (n=6), convulsions (n=5) and carbon monoxide intoxication (n=5). Of these, patients suffering cardiac arrest after convulsions had the best survival rate (40%), but this event had a low incident. After near-drowning (38%) and choking (23%), intoxications (19%) are the third most survivable cause of cardiac arrest in this group of patients (Kuisma & Alaspää 1997). In other studies, survival to discharge has ranged from 13% to 50% of intoxication patients when resuscitation was attempted (Paredes et al. 2004, Sloth-Madsen et al. 1984). In some cases, good neurological recovery has been reported even after prolonged cardiopulmonary resuscitation (CPR) (Rygnestad et al. 2005). In contrast, survival after cardiac arrest caused by opioid overdose has been reported to be either non-existent (Smith et al. 1992, Sporer et al. 1996) or phenomenally good (Bertini et al. 1992, Skulberg et al. 1993).
Consequences and complications of drug abuse and overdose
Opioid overdose related complications include death and recurrent opioid toxicity after treatment with opioid receptor antagonist. In addition, non-fatal overdoses can cause significant morbidity. The majority of drug users that had experienced an overdose were reported to have suffered from at least one complication (Warner-Smith M et al. 2002). The most important complications, related to loss of consciousness and extended immobility, are aspiration pneumonia and rhabdomyolysis (Table 3). Complications related to injecting drug use belong mainly to the realm of infectious diseases (Table 3). Direct mechanical damage to blood vessels (Coughlin & Mavor 2006) and lungs (Miller et al. 2006), foreign body embolus (Arnett et al. 1976, Low et al. 2006, Low & Nicol 2006, Rodriguez & Angeli 2006) and drug paraphernalia (“cotton fever”) related complications also occur (Harrison & Walls 1990). Although uncommon, cases of acute hepatitis after injecting use of buprenorphine have been reported (Berson et al. 2001), as has severe myositis (Seet & Lim 2006). Cases of spongiform leukoencephalopathy in individuals inhaling heroin fumes have been reported (Henry 2000, Nelson & Olsen 2010). After inhaling heroin vapors, bronchoconstriction resistant to inhaled β-sympathomimetics has been also reported (Cygan et al. 2000).
Table 3: Sequelae of opioid abuse.

Overdose

Overdose related
Aspiration pneumonia 1-4
Assaulted while unconscious 3
Burns 3
Cardiac arrest 1
Cardiac arrhythmias 3
Hypothermia 4
Injuries from falls 3
Ischemic cerebral insult 1, 4
Left ventricular dysfunction 4
Myocarditis 4
Peripheral neuropathy, temporary paralysis of limbs 3, 4
Pulmonary edema 1-5
Rhabdomyolysis 1, 3, 4
Seizures 3, 4
Vomiting 3

Injecting use related
Abscesses 2
Bloodborne infections 2, 6
Cellulitis 2
Endocarditis 2
Malaria 2
Pulmonary fibrosis, arteritis, granulomatosis 2 (rare)
Septic embolus (from injecting site) 2 and bacteremia 2
Tetanus 2
Thrombophlebitis 2

6. Kivelä et al. 2007
AIMS OF THE STUDY

1. To examine the characteristics and incidence of opioid overdose patients (II, III).

2. To examine the characteristics and incidence of overdose related to nonmedical use of buprenorphine (I).

3. To examine the incidence of γ-hydroxybutyrate and γ-butyrolactone overdoses involving injecting drug users (V).

4. To examine the incidence and time interval of recurrent opioid toxicity after prehospital naloxone administration in heroin overdose patients (III).

5. To examine the effects of naloxone administered during an opioid overdose on the cardiovascular system and catecholamine levels in piglets (IV).
MATERIALS AND METHODS

Description of the EMS system
Helsinki, the capital city of Finland, is a medium size city consisting of urban and suburban areas. At the end of 2007 it had a population of approximately 568,000, of which about 400,000 belonged to the 16-64 age group (Nyman et al. 2008). Especially during weekend evenings, there is a major influx of people due to the many restaurants and clubs in the city.

The emergency dispatching centre of Helsinki served the neighboring towns of Espoo, Kauniainen and Vantaa and townships of Kirkkonummi, Sipoo and Siuntio in addition to Helsinki itself until 1.12.2005. After 1.2.2006 it served only Helsinki. The total population of the area was over 1,000,000 by the end of the study period. The centre was responsible for dispatching medical, fire and rescue emergency calls. The dispatchers were full time professionals with one and a half years of formal training for handling emergency calls. Dispatching was criteria based, computer-aided and dispatching during event interrogation was routinely used. Dispatchers were able to guide the caller/s to give first aid to the patient, that is dispatcher assisted CPR and turning an unconscious patient to the recovery position. Priority dispatching was used in medical emergencies, and the prioritizing criteria were found in the dispatcher’s guidebook. Prioritizing was based on the patient’s chief complaint and current condition. According to this, the emergency call was placed into one of four urgency categories (A-D). Categories A-C were managed by the rescue department ambulances and category D by privately run non-emergency ambulances. In categories A and B, dispatching was immediate with blue lights and sirens and the target response time was 8 minutes. In category C dispatching was also immediate, but without blue lights and sirens, and the target response time was 20 minutes. Category D had a target response time of 90 minutes.

The EMS (i.e. ambulance service) of Helsinki is a physician led three tiered system responsible for urgent calls. The service provider is the rescue department of the city and the physicians are administratively under the Department of Anaesthesiology and Intensive care Medicine of the Helsinki University Central Hospital (HUCH). The physician on call participates in high risk calls with the mobile intensive care unit (MICU), being responsible for on-line medical direction and overall command of the EMS. Physicians are, together with the service provider representatives, also responsible for off-line medical direction, education and quality improvement programs in the EMS system. During the study period, the physician managed over 12,000 telephone consultations and the physician staffed MICU participated in over 2,000 calls annually.

The ambulances of the rescue department are situated in eight fire stations and one ambulance station. As first responding units, fire engines are also used if necessary. The first tier is staffed by emergency medical technicians (EMTs) capable of starting an intravenous line and intubating an adult cardiac arrest victim. The first tier consists of eight ambulances and fire engines. The second tier consists of three advance life support units (ALS) and a medical
supervisor unit. These units are manned by EMTs with advance life support training and are able to administer intravenous medication, including naloxone. The third tier is the MICU staffed by two EMTs and a physician. The EMS also registers all sudden out-of-hospital deaths in the city.

Patients were transported to two secondary and two tertiary care hospitals (one for adult and one for pediatric patients) (I, II, III, and V).

**Data collection**
Studies I-III and V were retrospective. Approval of both Helsinki University Central Hospital (HUCH) Ethics Committee and the head of department were obtained. The EMS records of patients with presumed opioid overdose or intoxication were retrieved for studies I and III. Criteria by which patients were considered to have an opioid overdose or intoxication were either witnessed opioid use or circumstantial evidence of drug use and symptoms and signs of an opioid overdose. Symptoms and signs of an opioid overdose were considered to be miosis, decreased level of consciousness and respiratory depression. For the purpose of this study we considered patients with a Glasgow Coma Score (GCS) of 8 or less to be an overdose case, even if signs of hypoventilation were not recorded. Patients that were sedated without signs of respiratory depression were considered to be opioid intoxications. Patients with signs of hypoventilation or and who were unresponsive when the emergency dispatching centre was called were also considered to be overdose cases. Signs of respiratory depression were considered to be: respiratory rate less than 12/min, peripheral oxygen saturation lower than 90% without supplemental oxygen (or <95% with supplemental oxygen) or cyanosis on the arrival of the first responding unit. Patients were considered to be naloxone responders if their GCS improved (> 8) and/or respiratory rate was more than 12/min and peripheral oxygen saturation was over 90% after naloxone administration.

Patients with overdose related to nonmedical use of buprenorphine between 1.1.1995 and 30.4. 2002 were included in the study (I). Patients with presumed heroin overdose between 1.1.1995 and 31.12.2000 were included in the study (III). In this study, the hospital records were also retrieved. The data of the overdose patients treated by the EMS and left on scene were compared with the data from the medical examiner and cardiac arrest registry. When comparing the EMS records to the records of the medical examiner, the name, sex, date of birth, social security number and date and time of the overdose or death were used as reference. Although the users of other drugs, medicines and alcohol and the users of opioids other than heroin were excluded from the published study, these patients were included in this thesis. Also included were previously unpublished data on the incidence of presumed opioid overdose in 2001-2007 and comparison of the characteristics of buprenorphine and heroin overdose patients in 1995-2005.

Patients with overdose or poisoning as the cause of cardiac arrest were identified from the cardiac arrest database between 1.1.1997 and 31.12.2000 (II). The cardiac arrest database is population based and the data are prospectively collected in Utstein style (Cummins et al. 1991). Cardiac arrest was defined as the lack of signs of mechanical cardiac activity;
unresponsiveness, respiratory arrest or agonal respirations and the absence of a palpable pulse. The verification of the etiology of cardiac arrest was obtained from autopsy reports and/or hospital records.

The EMS records of patients with serious presumed GHB or GBL overdoses were retrieved from January 1st 2006 to December 31st 2007 for study V. Patients included in the study had symptoms and signs of a GHB/GBL overdose and either a history of recent GHB/GBL use or GHB/GBL was found on their person. Symptoms and signs of a GHB/GBL overdose were a reduced level of consciousness with periods of agitation, respiratory depression and bradycardia (Li et al. 1998 II, Snead et Gibson 2005). If the patient had a reduced level of consciousness and/or respiratory depression, the overdose was considered to be serious. The possible confirmation of the diagnosis of GHB/GBL overdose, level of care required in the ED, disposition and previous substance abuse were obtained from the hospital records.

The date and time of the call to the emergency dispatching centre, age, sex, previous substance abuse, agents involved in current overdose, level of consciousness and respiration on arrival of the first responding unit and after treatment, treatment provided by the EMS personnel and disposition were recorded for each patient. When patient cooperation was adequate, alcohol breath analyzers were used in the prehospital phase (Dräger alcotest 6510, Drägerwerk AG & Co. KGaA 23542 Lübeck, Germany).

Cardiovascular changes after naloxone administration in propofol-sedated piglets during opioid overdose: study protocol (IV)

The HUCH animal research board and the head of department approved the study. In order to establish the dose of morphine able to cause respiratory depression and the dose of naloxone capable of reversing it, six unpremedicated domestic piglets were used (weight 17-24 kg). Each piglet received a morphine dose double that of the previous piglet, if there had been no sign of respiratory depression such as reduced respiratory rate. The naloxone dose used was 80 µg/kg. The dose was comparable to the highest total dose (6 mg) of naloxone used in the prehospital care of heroin overdose patients in a study by Vilke et al. (Vilke et al. 2003). Eight unpremedicated animals of the same size as those used for finding the dose were used for the experiment.

An ear vein was cannulated for i.v. access, through which propofol was used to induce general anesthesia. Propofol infusion was started at a rate that kept the animals spontaneously breathing and non-responsive to moderate physical stimuli. The piglets were intubated, after which adequate oxygenation was ensured by directing an oxygen flow of 2-3 l/min into the intubation tube while surgical preparations were made. Plain lidocaine 10 mg/ml was used to infiltrate all sites of surgical preparations or punctures, 2-3 ml per site. One of the femoral arteries was cannulated for continuous blood pressure measurement and blood sampling. A 5F pulmonary artery catheter (Swan-Ganz catheter, Edwards Lifesciences Co, Irvine, Ca, USA) was inserted through one of the internal jugular veins for measurement of pulmonary arterial pressures. Transthoracic ECHO (Sonos 5500, Philips, USA) was used to assess baseline cardiac function.
Baseline values for vital functions, including heart rate, cardiac rhythm, systemic blood pressure (systolic, diastolic and mean values), mean pulmonary arterial pressure (MPAP), peripheral oxygen saturation, breath rate and end tidal carbon dioxide (CO₂) were recorded every 30 seconds after oxygen flow was discontinued. Baseline samples for catecholamine (norepinephrine and epinephrine) concentration and arterial blood gas determination were also obtained. After this, morphine (8 mg/kg) was injected into the central venous line in 4 seconds. Transthoracic ECHO was used for the continuous assessment of cardiac performance and vital functions were recorded every 30 seconds. Five and ten minutes after the injection of the opioid, arterial blood gases were measured and a sample for the analysis of plasma catecholamines was drawn at ten minutes. Ten minutes after the administration of morphine, or earlier if the animal became hypoxic and bradycardic (heart rate < 50/min), naloxone 80 µg/kg (Narcan®, 0.4 mg/ml, Dupont, Meda) was administered i.v. Five and ten minutes after the administration of naloxone, arterial blood gases were measured and ten minutes after the administration of naloxone samples for the analysis of plasma catecholamine concentrations were drawn. The study protocol is presented in Figure 1. Throughout the experiment, the i.v.-propofol infusion was continued at the same rate as at the time of the recording of the baseline values. After completing the experiment, the animal was sacrificed by injecting 20 ml of KCl (Addex-Kaliumklorid® 150 mg/ml, Fresenius Kabi) intracardially.

**Figure 1:** Study protocol for study IV.

<table>
<thead>
<tr>
<th>Arterial blood gases</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamines</td>
<td>0 min</td>
</tr>
<tr>
<td>Morphine 8 mg/kg i.v.</td>
<td>Baseline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arterial blood gases</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamines</td>
<td>5 min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arterial blood gases</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamines</td>
<td>10 min</td>
</tr>
<tr>
<td>Naloxone 80 microg/kg i.v.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arterial blood gases</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamines</td>
<td>15 min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arterial blood gases</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamines</td>
<td>20 min</td>
</tr>
</tbody>
</table>

Heart rate, mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), peripheral oxygen saturation (SpO2%), and end tidal carbon dioxide (eTCO₂) were recorded at 30 second intervals and transthoracic echocardiograph was continuously recorded.
Echocardiographic measurements
The echocardiography measurements were performed using a two MHz transthoracic sector transducer through the parasternal acoustic window. The left ventricle’s end-systolic and end-diastolic internal diameters were measured at midpapillary level. The left ventricular ejection fraction was defined using the M-mode acquisition and the standard Teicholz formula. The mean of three sequential heart cycles were used for each stage. The acquisitions were stored digitally on a magneto-optic disc and the measurements were made off-line.

Assay of catecholamines
The blood samples were drawn into ice-cold EDTA-tubes and immediately centrifuged and plasma was separated and stored at -70 °C. High performance liquid chromatography using electrochemical detection (HPLC-EC) (Coullochem III, ESA, Inc., Chelmsford, MA) was used to determine the plasma concentrations of norepinephrine and epinephrine. The method was a modification from the HPLC-EC method used in the study by Yli-Hankala et al. (Yli-Hankala et al 1993) to assay catecholamine levels in human plasma. Catecholamines were extracted with activated alumina (Alumina for column chromatography, Activity grade I, Type WA-I: Acid, Sigma Chemical Co., St-Louis, MO). The mobile phase contained 50 mM H$_3$PO$_4$, 50 mM citric acid, 100 mg/L SDS, 40 mg/L Na-EDTA, and methanol (15% v/v in the final solution), with the pH adjusted to 3.0 with NaOH. A reversed-phase Inertsil ODS-3 (5µm, 4.6 x 250 mm; GL Sciences Inc., Tokyo, Japan) column was used. Limit of quantitation was set at 0.10 ng/ml for both norepinephrine and epinephrine. The intra-assay repeatability, expressed as the relative standard deviation (RSD), was approximately 6% for both the analytes at the concentration level of 1.00 ng/ml (n = 8).

Statistical methods
Data were analyzed using SPSS statistical software (SPSS for Windows version 11.5.1, 14.0, 16.0 or 17.0 SPSS Inc., Chicago, IL, USA). Due to small sample size, non-parametric tests were used. Median and interquartile range were presented for continuous data, which were analyzed by the Mann-Whitney U test (II, V) or Friedman’s statistic (IV) and Wilcoxon signed rank tests (IV). Categorical variables were analyzed using chi-square (II, V) or Fisher’s exact test (II). The level of significance was set at p < 0.05.
RESULTS

Intoxications and overdoses treated by Helsinki EMS in 1995-2007
Helsinki EMS ambulances were dispatched annually to 34,153-45,118 calls from 1995 to 2007. Seven to eight percent of them were coded as intoxications or overdoses regardless of origin. The annual number of presumed non-fatal opioid overdoses treated by Helsinki EMS undulated greatly between 1995 and 2007 (Fig. 2, unpublished data). The annual number of GHB/GBL related overdose patients treated by Helsinki EMS steadily increased from 21 to 73 between 2004-2007 (unpublished data).

Figure 2: Incidence/year of presumed non-fatal opioid overdoses treated by Helsinki Emergency Medical Service from 1.1.1995 to 31.12.2007 (unpublished data).

Presumed opioid overdose patients treated by Helsinki EMS in 1995-2005
There were 391 patients identified with presumed opioid overdose treated by Helsinki EMS from 1.1.1995 to 31.12.2005. Four patients were excluded because EMS records had insufficient data. There appeared to be a peak in incidence on weekend evenings (Fig. 3 and 4, unpublished data) and the majority (64%) of patients had reportedly used heroin (Fig. 2, unpublished data). Patients were predominately male, with a median age of 28 years (22;33, 25- and 75- quartiles, respectively). In addition to opioids, the use of other substances, mainly alcohol and/or benzodiazepines, was reported in 36% of patients (Table 4, unpublished data). Fifty five percent of the patients required ventilatory support in the prehospital phase. This was either by
bystander CPR, bag-mask ventilation or intubation. Naloxone was administered by the EMS in 84% of the cases (Table 4, unpublished data). Both in the beginning and in the end of the time period the majority of patients were transported to an emergency department (ED) for further care (Fig. 5, unpublished data).

**Figure 3:** Incidence/weekday of presumed opioid overdoses. Patients treated by Helsinki Emergency Medical Service from 1.1.1995 to 31.12.2005 (unpublished data).

**Figure 4:** Incidence/time of day of presumed opioid overdoses. Patients treated by Helsinki Emergency Medical Service from 1.1.1995 to 31.12.2005 (unpublished data).
Table 4: Characteristics of presumed opioid overdose or intoxication patients treated by Helsinki Emergency Medical Service from 1.1.1995 to 31.12.2005 (unpublished data).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>387</td>
</tr>
<tr>
<td>Age (years)¹</td>
<td>28 (22;33)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>324 / 63</td>
</tr>
<tr>
<td>Polydrug use (%)</td>
<td>139 (35.9%)</td>
</tr>
<tr>
<td>Prehospital care</td>
<td></td>
</tr>
<tr>
<td>Ventilatory support (%)</td>
<td>211 (54.5)</td>
</tr>
<tr>
<td>Naloxone administration (%)</td>
<td>323 (83.5)</td>
</tr>
<tr>
<td>Naloxone dose (mg)¹</td>
<td>0.4 (0.4;0.72)</td>
</tr>
</tbody>
</table>

¹ Median, 25- and 75-quartiles in parentheses.

Figure 5: Primary disposition (left on scene vs. transported) of presumed opioid overdose patients treated by Helsinki Emergency Medical Service from 1.1.1995 to 31.12.2005 (unpublished data).
Serious overdoses involving buprenorphine in Helsinki (I)
Helsinki EMS treated 12 buprenorphine related overdose patients in 1995-2002. One patient was excluded because he had no signs of respiratory depression and a GCS of 11. All the remaining patients except one were male and their median age was 24 years (range 20-30 years). In the first two cases Temgesic® was the preparation used, but since 2000 Subutex® was used. Buprenorphine was used intravenously in seven cases and orally in one of the cases. The route was not recorded in the remaining three cases. There was concomitant use of benzodiazepines in three cases, ethanol in four and heroin in two. On arrival of the EMS, nine of the patients had either a reduced level of consciousness or/and signs of respiratory depression. One patient was sedated. In one case, the associates of an opioid user reportedly had administered buprenorphine (in the form of crushed and dissolved Subutex® tablets) intravenously to their friend after he had suffered from a heroin overdose. He had a GCS of 15 and no signs of respiratory distress on arrival of the first responding unit. All patients were administered naloxone by the EMS, and the median dose of naloxone was 0.4 mg (range 0.2-0.8 mg). Only one of the patients did not respond to naloxone and he was intubated and transported to an ED (Study I: Table 1).

Table 5: Comparison of heroin and buprenorphine related overdose patients treated by Helsinki Emergency Medical Service from 1.1.1995 to 31.12.2005 (unpublished data).

<table>
<thead>
<tr>
<th></th>
<th>Heroin</th>
<th>Buprenorphine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)¹</td>
<td>(n=247)</td>
<td>(n=27)</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>27 (21;33)</td>
<td>26 (23;31)</td>
<td>0.971</td>
</tr>
<tr>
<td>Signs of respiratory depression, n (%)</td>
<td>207 (83.8)</td>
<td>25 (93)</td>
<td>0.229</td>
</tr>
<tr>
<td>Yes</td>
<td>211 (85.4)</td>
<td>18 (67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>15 (6.1)</td>
<td>9 (33)</td>
<td></td>
</tr>
<tr>
<td>Unrecorded</td>
<td>21 (8.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Score, n (%)</td>
<td></td>
<td></td>
<td>0.098</td>
</tr>
<tr>
<td>≤ 8</td>
<td>188 (76.1)</td>
<td>18 (67)</td>
<td></td>
</tr>
<tr>
<td>&gt; 8</td>
<td>45 (18.2)</td>
<td>9 (33)</td>
<td></td>
</tr>
<tr>
<td>Unrecorded</td>
<td>14 (5.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Polydrug use, n (%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>82 (33.2)</td>
<td>19 (70)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>101 (40.9)</td>
<td>6 (22)</td>
<td></td>
</tr>
<tr>
<td>Unrecorded</td>
<td>64 (25.9)</td>
<td>2 (7)</td>
<td></td>
</tr>
</tbody>
</table>

¹ Median values (25 and 75 percentiles in parentheses).

Comparison of buprenorphine and heroin related overdose
After the initial patients, Helsinki EMS treated fifteen buprenorphine overdose patients in 2002-2005. The relative incidence of buprenorphine related overdoses increased as the total number of opioid overdoses decreased after 2001, except for 2004 (Fig. 2, unpublished data). Subutex ® tablets were reportedly used in all the cases. The tablets were crushed, dissolved and
injected i.v. There was concomitant use of other central nervous system depressants, mainly alcohol and benzodiazepines, in 70% of the buprenorphine related overdoses (Table 5, unpublished data). During the same time period, Helsinki EMS treated 247 patients with reported heroin overdose: in comparison to the buprenorphine users, they had less polydrug use (33%). Although heroin and buprenorphine users had a similar incidence of low level of consciousness (Glasgow Coma Score ≤ 8), heroin users presented signs of respiratory depression more often (Table 5, unpublished data).


<table>
<thead>
<tr>
<th></th>
<th>Not transported</th>
<th>Transported</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>102</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>Sex (m/f) (%)</td>
<td>91/11 (89/11)</td>
<td>131/32 (80/20)</td>
<td>0.061</td>
</tr>
<tr>
<td>Age7</td>
<td>27 (21;32)</td>
<td>27 (22;31)</td>
<td>0.740</td>
</tr>
<tr>
<td>MICU present (%)</td>
<td>89 (87)</td>
<td>142 (87)</td>
<td>1.000</td>
</tr>
<tr>
<td>Polydrug use recorded (%)</td>
<td>17 (17)</td>
<td>82 (50)</td>
<td>0.111</td>
</tr>
<tr>
<td>Ventilatory support (%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>8 (8)</td>
<td>6 (4)</td>
<td></td>
</tr>
<tr>
<td>Bag-valve-mask</td>
<td>57 (56)</td>
<td>65 (40)</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>3 (3)</td>
<td>27 (17)</td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>34 (33)</td>
<td>64 (40)</td>
<td></td>
</tr>
<tr>
<td>Naloxone given (%)</td>
<td>74 (73)</td>
<td>135 (83)</td>
<td>0.046</td>
</tr>
<tr>
<td>Naloxone dose (mg)7</td>
<td>0.40 (0.32;0.40)</td>
<td>0.40 (0.24;0.48)</td>
<td>0.730</td>
</tr>
<tr>
<td>Refused further care and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were left on scene</td>
<td>95 (93)</td>
<td>61 (37)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>26 (16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>55 (34)</td>
<td></td>
</tr>
<tr>
<td>Taken into police custody</td>
<td>6 (6)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Taken to a drug rehabilitation Center</td>
<td>1 (1)</td>
<td>Excluded from final study2</td>
<td>18 (11)</td>
</tr>
</tbody>
</table>

MICU: mobile intensive care unit, GCS: Glasgow Coma Score, CPR: cardiopulmonary resuscitation, ED: emergency department, AMA: against medical advice.

1) Age and naloxone dose presented as median (25- and 75-quartiles in parentheses).

2) Patients excluded from final study (in addition to polydrug users and patients using opioid other than heroin): 12 patients: no hospital records found, 6 patients: leave ED immediately on arrival.
Recurrent opioid toxicity after prehospital care of presumed heroin overdose patients (III)
Between 1.1.1995 and 31.12.2000, 269 presumed opioid overdose patients were treated by Helsinki EMS. Of them, 102 patients were treated on scene and released (n=95), left to police custody (n=6) or transported to a drug rehabilitation centre (n=1). Four patients were excluded because of insufficient data on the EMS form. Patient characteristics are presented in Table 6 (unpublished data). Of the 102 patients, 84 had reportedly used only heroin. The remaining 18 patients had polydrug use or had used another opioid than heroin and were excluded from study III (Table 7, unpublished data, Fig. 6).


<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Frequency (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin + alcohol</td>
<td>38 (37.6%)</td>
</tr>
<tr>
<td>Heroin + benzodiazepines</td>
<td>34 (33.7%)</td>
</tr>
<tr>
<td>Heroin + alcohol + benzodiazepines</td>
<td>7 (6.9%)</td>
</tr>
<tr>
<td>Heroin + unknown</td>
<td>7 (6.9%)</td>
</tr>
<tr>
<td>Heroin + amphetamine</td>
<td>3 (2.9%)</td>
</tr>
<tr>
<td>Heroin + buprenorphine</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Buprenorphine (IV) + alcohol + benzodiazepines</td>
<td>3 (2.9%)</td>
</tr>
<tr>
<td>Heroin + amphetamine + benzodiazepines</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Buprenorphine + alcohol</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Buprenorphine (IV) + benzodiazepines</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Buprenorphine (IV)</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Dextropropoxyphene (IV)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Unknown polydrug use</td>
<td>1 (0.9%)</td>
</tr>
</tbody>
</table>

IV: intravenous.

Of the excluded patients, one was found with advanced signs of death 5 hours and 44 minutes after refusing further care and being left on the scene. In autopsy his death was considered to be due to a heroin overdose with concomitant alcohol use. He had signs of hypoventilation and a GCS of 8 or less on arrival of the first responding unit, but regained consciousness with bag-mask ventilation and was not administered naloxone.

In addition to the patient mentioned above, five other patients that were treated by the EMS for opioid overdose and left on scene were found with advanced signs of death. There was at least, however, five weeks difference between being treated by the EMS and the time of death. Heroin was involved in three deaths (polydrug or ethanol use in two of them), amphetamine alone in one and suicide by hanging in one.

After prehospital care, 163 patients were transported to an ED (Table 6, unpublished data). Eighteen (18) patients were excluded, six because they escaped immediately after arrival at the ED and 12 because no hospital records were retrieved. From the remaining 145 patients, 84 were excluded.
from the final study because of polydrug use or the use of other opioids than heroin (Table 7, unpublished data, Fig. 6).

Among the excluded patients, 29 were administered naloxone in the ED because of respiratory depression. Of them, 22 had a GCS below 15 or/and signs of respiratory distress already on arrival at the ED. Five of the seven remaining patients had received naloxone prehospitaly. The time intervals between prehospitaly and ED administered naloxone were 100, 104 and 173 min. The time intervals were not available in two cases. One patient developed pulmonary edema. Other opioid use related adverse events that were recorded in the patients transported to an ED are presented in Table 8 (unpublished data).

**Patients included in the study (III)**
The characteristics of the 145 presumed heroin overdose patients included in this study are presented in Table 9. Most (83%) were males and median age was 26 years (21;32, 25- and 75-quartiles, respectively). When reported, the route of heroin administration was intravenous. While the majority (92%) of patients showed signs of respiratory depression and/or had a GCS ≤ 8, six had been unresponsive or had signs of respiratory depression when the emergency dispatching centre was called and five patients were only sedated on arrival of the first responding unit. After prehospital care by the EMS, 84 patients refused further care and were not transported to an ED: however the remaining 61 patients were transported to an ED.

Seventy one (85%) of the patients that were not transported to an ED were administered naloxone by the EMS. Eight patients recovered by ventilatory assistance alone and five recovered spontaneously. During a 12-hour follow up
Table 8: Adverse events (other than respiratory depression) and disposition of presumed opioid overdose patients transported to an emergency department from 1.1.1995 to 31.12.2000 (unpublished data).

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Heroin only</th>
<th>Polydrug use</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>Heroin only</td>
<td>Polydrug use</td>
<td>p-value</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>4 (7%)</td>
<td>3 (4%)</td>
<td>0.444</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1 (2%)</td>
<td>2 (2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>1 (2%)</td>
<td>3 (4%)</td>
<td>0.639</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
<td>0.573</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.421</td>
</tr>
<tr>
<td>Previously diagnosed</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.421</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>2 (2%)</td>
<td>0.509</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>0</td>
<td>1 (1%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Suspected skull base</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disposition

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Heroin only</th>
<th>Polydrug use</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>29 (47.5%)</td>
<td>32 (38.1%)</td>
<td>0.307</td>
</tr>
<tr>
<td>Left AMA</td>
<td>8 (13.1%)</td>
<td>18 (21.4%)</td>
<td>0.273</td>
</tr>
<tr>
<td>Admitted</td>
<td>23 (37.7%)</td>
<td>32 (38.1%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Transported to</td>
<td>1 (1.6%)</td>
<td>2 (2.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>secondary hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time in ED (outpatients) 5.6 (2.5;9.4) 8.2 (5.9;13.4) 0.040

1) Median (25 and 75 percentiles in parentheses).
AMA: against medical advice; ED: emergency department.

Table 9: The characteristics of 145 patients treated by Helsinki Emergency Medical Service for presumed heroin overdose from 1.1.1995 to 31.12.2000. The results are presented as numbers (% in parentheses) or as medians with 25- and 75-quartiles in parentheses (Study III).

<table>
<thead>
<tr>
<th>n</th>
<th>145</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>120 (82.8%) / 25 (17.2%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26 (21;32)</td>
</tr>
<tr>
<td>Heroin route IV</td>
<td></td>
</tr>
<tr>
<td>Sniffed</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Smoked</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Unreported</td>
<td>97 (66.9%)</td>
</tr>
<tr>
<td>Emergency physician on scene</td>
<td>124 (86.7%)</td>
</tr>
<tr>
<td>Respiratory depression or/and</td>
<td>134 (92.4%)</td>
</tr>
<tr>
<td>GCS ≤ 8 on arrival of FRU</td>
<td></td>
</tr>
</tbody>
</table>

IV: intravenously; GCS: Glasgow Coma Score; FRU: first responding unit.
period, none of the aforementioned patients that were administered naloxone suffered from severe recurrent opioid toxicity. One patient sustained cardiac arrest and was successfully resuscitated while in police custody. Seven hours previously he had been treated by EMS personnel. He had been found unconscious and cyanotic in a service station toilet. After being intubated and ventilated by the EMS personnel, he regained consciousness and subsequently fled from the scene before naloxone was administered. In hospital, after recovering from cardiac arrest, he admitted smoking heroin. One patient was treated and transported to an ED by the EMS four hours and thirty minutes after the initial call by EMS. She had no signs of hypoventilation and she had a GCS of 14 during the second call.

Sixty one patients were transported to an ED, 52 of which were administered naloxone by the EMS prior to transportation. After prehospital care, 30 (49%) patients still had signs of opioid toxicity. Two patients were transported intubated. Twelve patients had recorded signs of respiratory depression in the ED and were administered inpatient naloxone; seven of which had a GCS of 15 and no signs of respiratory distress recorded immediately after prehospital care. In the ED, nine of the twelve patients that were administered inpatient naloxone had signs of opioid toxicity and one was mildly hypothermic ( tympanic membrane temperature 35 °C) on arrival at the ED. Two patients suffered from other adverse events related to opioid use (aspiration pneumonia and rhabdomyolysis). Although all events were evident within one hour of arrival at the ED, the median time interval between prehospital and inpatient administered naloxone was 102 min (25-and 75-percentile: 77;187). The median time interval from prehospital naloxone administration to arrival at the ED was 42 min (25-and 75-percentile: 30;50). In addition to the twelve patients mentioned above, three patients were administered naloxone in the ED without any recorded signs of respiratory depression.

Prehospitaly administered s.c. or i.m. naloxone and recurrent respiratory depression
The majority (55.3%) of patients were administered at least part of the naloxone dose i.m. or s.c. Of the 52 patients that were administered naloxone by the EMS and transported to an ED, 16 patients were administered prehospital naloxone i.m. or s.c. Two (13%) of them were administered naloxone in the ED. Their total prehospital naloxone doses were 0.6 mg and 0.8 mg and the time intervals between prehospital and inpatient administered naloxone were 233 and 104 minutes, respectively. In contrast, of the 36 patients that did not receive any prehospital naloxone i.m. or s.c., thirteen (36%) were administered naloxone in the ED (2/16 vs. 13/36, p= 0.106). Three of the thirteen patients did not have signs of respiratory depression recorded, however, before naloxone administration in the ED. There was a statistically significant difference in naloxone dosage
between the two groups of patients: median, 25-and 75-percentile 0.4 (0.4;0.6) mg versus 0.3 (0.2;0.4) mg, p=0.006, prehospital naloxone s.c./i.m. versus prehospital naloxone only i.v. respectively. The time interval between prehospital and inhospital naloxone administration was 85 (76;126) min (median, 25-and 75-percentile) in the group of patients that received prehospital naloxone only i.v. (Boyd, unpublished data).

Prehospital and inhospital naloxone doses are presented in Table 10. When administered prehospital, the total naloxone dose was up to 0.8 mg in 99% of the patients. After prehospital naloxone, hypertension (n=1), tachycardia (n=1), aggressive behavior (n=3), vomiting (n=3) and shivering (n=1) were recorded in the patients (unpublished data). Inhospital naloxone was administered to seven patients more than once and two received a naloxone infusion. All patients that were administered naloxone in the ED responded to it.

**Table 10:** Naloxone doses and routes of administration in patients with presumed heroin overdose treated by Helsinki Emergency Medical Service from 1.1.1995 to 31.12.2000 (Study III).

<table>
<thead>
<tr>
<th>Prehospital naloxone dose (n=123)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 mg</td>
<td>36 (29.3)</td>
</tr>
<tr>
<td>0.4 – 0.8 mg</td>
<td>87 (70.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prehospital routes of administration (n=123)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only IV</td>
<td>46 (37.4)</td>
</tr>
<tr>
<td>Only IM or SC</td>
<td>35 (28.5)</td>
</tr>
<tr>
<td>IV and IM or SC</td>
<td>33 (26.8)</td>
</tr>
<tr>
<td>Route not recorded</td>
<td>9 (7.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ED naloxone dose (all administered IV) (n=12)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 mg</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>0.4 – 0.8 mg</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Infusion</td>
<td>2 (16.7)</td>
</tr>
</tbody>
</table>

ED: emergency department; IV: intravenously; IM: intramuscularly; SC: subcutaneously
GHB/GBL overdoses involving injecting drug users in Helsinki (V)
The records of 100 GHB/GBL overdose patients were retrieved from 2006-2007. The incidence of GHB/GBL overdoses involving injecting drug users increased from 18 to 31 patient contacts from 2006 to 2007. Figures 7 and 8 present the temporal distribution of the patients according to the weekday and the time of day, respectively. Thirty nine patient contacts were on Friday-Saturday or Saturday-Sunday night between 11 pm-6 am (Group C). Sixty one of the patient contacts were outside this timeframe (Group D). Nearly all the patients were encountered in the city centre, an area North-east of the city centre (Kallio) or in areas in their immediate vicinity.

**Figure 7:** Patients with serious GHB and GBL overdose treated by Helsinki Emergency Medical Service in 2006 -2007. Distribution of overdoses according to the day of the week (Study V).

![Graph showing distribution of overdoses by day of the week.](image)

GHB: gamma-hydroxybutyrate, GBL: gamma-butyrolactone.

**Figure 8:** Patients with serious GHB and GBL overdose treated by Helsinki Emergency Medical Service in 2006 -2007. Distribution of overdoses according to the time of day (Study V).

![Graph showing distribution of overdoses by time of day.](image)

GHB: gamma-hydroxybutyrate, GBL: gamma-butyrolactone.
Patient characteristics, naloxone and flumazenil administration are presented in Table 11 and concomitantly used drugs and medications in Table 12. Between the two groups there were statistically significant differences in the history of chronic injecting drug use (p=0.012), reported concomitant use of other substances (p=0.028) and, in particular, concomitant ethanol use (p=0.019). Injecting drug users had a history of serious substance abuse including amphetamine, heroin and/or buprenorphine use. No statistically significant differences were noted in the administration of naloxone and flumazenil, a benzodiazepine antagonist, between the two groups (p= 0.083). None of the patients responded to naloxone administration. GCS increased markedly in two patients in both groups after flumazenil administration. Eight (21%) versus 14 (23%) (group C vs. D, respectively) patients were intubated on scene by EMS (p=0.774).

**Table 11:** Patient characteristics and antagonist administration. Patients with serious GHB and GBL overdose treated by Helsinki Emergency Medical Service in 2006 - 2007. Group C: call to emergency dispatching centre made on Friday-Saturday or Saturday-Sunday night between 11 pm and 6 am. Group D: call to emergency dispatching centre made at other times (Study V).

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group D</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>39</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>19 (49%)</td>
<td>35 (57%)</td>
<td>0.397</td>
</tr>
<tr>
<td>Age*</td>
<td>24 (22;27)</td>
<td>25 (23;29)</td>
<td>0.134</td>
</tr>
<tr>
<td>History of injecting drug use</td>
<td>13 (33%)</td>
<td>36 (59%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Antagonist administration</td>
<td></td>
<td></td>
<td>0.083</td>
</tr>
<tr>
<td>- naloxone</td>
<td>0</td>
<td>5 (8%)</td>
<td></td>
</tr>
<tr>
<td>- flumazenil</td>
<td>6 (15%)</td>
<td>5 (8%)</td>
<td></td>
</tr>
<tr>
<td>- flumazenil and naloxone</td>
<td></td>
<td>1(2%)</td>
<td></td>
</tr>
</tbody>
</table>

*Median and percentiles
GHB: gamma-hydroxybutyrate, GBL: gamma-butyrolactone.

There were statistically significant differences between the two groups in the location where the EMS encountered the patient (private vs. public indoors vs. outdoors, p=0.019) and whether GHB/GBL use was self reported, reported by bystanders/associates or based on clinical suspicion, p=0.023 (Table 13). After prehospital evaluation and care, practically all patients (99%) were transported after prehospital care to one of the three hospitals EDs of the city.
**Table 12:** Concomitantly used illicit or licit drugs and ethanol in GHB/GBL overdose. Patients with serious GHB and GBL overdose treated by Helsinki Emergency Medical Service in 2006 -2007. Group C: call to emergency dispatching centre made on Friday-Saturday or Saturday-Sunday night between 11 pm and 6 am. Group D: call to emergency dispatching centre made on other times (Study V).

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Group C</th>
<th>Group D</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall use of other drugs or ethanol</td>
<td>31 (80%)</td>
<td>38 (62%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Ethanol</td>
<td>29 (74%)</td>
<td>31 (51%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>3 (10%)</td>
<td>5 (13%)</td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td>2 (7%)</td>
<td>5 (13%)</td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td>6 (19%)</td>
<td>4 (11%)</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>MDMA 'Ecstasy'</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Unknown tablets</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Antidepressant drug</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

MDMA: 3,4-methylenedioxyamphetamine

**Table 13:** Emergency call and characteristics of overdose. Patients with serious GHB and GBL overdose treated by Helsinki Emergency Medical Service in 2006 -2007. Group C: call to emergency dispatching centre made on Friday-Saturday or Saturday-Sunday night between 11 pm and 6 am. Group D: call to emergency dispatching centre made on other times (Study V).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group C</th>
<th>Group D</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>39</td>
<td>61</td>
<td>0.687</td>
</tr>
<tr>
<td>Call to Emergency Dispatching Center</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-associate, relative</td>
<td>16 (41%)</td>
<td>25 (41%)</td>
<td></td>
</tr>
<tr>
<td>-by passer</td>
<td>8 (21%)</td>
<td>9 (15%)</td>
<td></td>
</tr>
<tr>
<td>-police</td>
<td>11 (28%)</td>
<td>21 (34%)</td>
<td></td>
</tr>
<tr>
<td>-not recorded</td>
<td>4 (10%)</td>
<td>6 (10%)</td>
<td></td>
</tr>
<tr>
<td>Patient encountered by EMS</td>
<td></td>
<td></td>
<td>0.019</td>
</tr>
<tr>
<td>-inside, private</td>
<td>4 (10%)</td>
<td>15 (25%)</td>
<td></td>
</tr>
<tr>
<td>-inside, public</td>
<td>16 (41%)</td>
<td>11 (18%)</td>
<td></td>
</tr>
<tr>
<td>-outdoors</td>
<td>16 (41%)</td>
<td>32 (53%)</td>
<td></td>
</tr>
<tr>
<td>-not recorded</td>
<td>3 (8%)</td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td>Information on GHB or GBL use</td>
<td></td>
<td></td>
<td>0.023</td>
</tr>
<tr>
<td>-history (patient, associates)</td>
<td>28 (72%)</td>
<td>52 (85%)</td>
<td></td>
</tr>
<tr>
<td>-signs and symptoms and paraphelia</td>
<td>11 (28%)</td>
<td>6 (10%)</td>
<td></td>
</tr>
<tr>
<td>-not recorded</td>
<td></td>
<td>3 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

GHB: gamma-hydroxybutyrate, GBL: gamma-butyrolactone.
Outcome after heroin overdose and cardiopulmonary resuscitation (II)
The study period was from 1.1.1997 to 31.12.2000. During this time, the EMS treated 8604 intoxication patients, of which 131 (1.5%) required ventilatory support. During the same time period, altogether 241 presumed opioid overdose patients were also treated. Of them, 134 (55.6%) required ventilatory support. Also, ninety four patients were in cardiac arrest due to acute drug poisoning / overdose and considered for resuscitation (Fig. 9). In the cases when resuscitation was attempted, drug etiology of the cardiac arrest is presented in Table 14. Cardiac arrest was caused by a heroin overdose in 19 (Group A), and by other agents in 53 (Group B), of these patients (Table 14, Fig. 9). Patient characteristics are presented in Table 15.

**Figure 9:** Cardiac arrest patients treated by Helsinki Emergency Medical Service from 1.1.1997 to 31.12.2000. Group A (cardiac arrest caused by heroin overdose) and group B (cardiac arrest caused by acute drug poisoning by agents other than heroin) (Study II).

The call to dispatching time delay was similar in both groups (Table 16). The dispatcher provided dispatcher assisted CPR in 4 versus 16 cases but bystander CPR was given to 6 versus 14 patients (Group A vs. B, respectively). In group A, mouth-to-mouth ventilation and chest compressions were given to five patients and only mouth-to-mouth ventilation to one patient. In group B, mouth-to-mouth ventilation and chest compressions were given to seven, only mouth-to-mouth ventilation to four and only chest compressions to three patients.

Cardiac arrest was not recognized by emergency dispatching centre or patients suffered from it after the call in 6 (32%) versus 21 (40%) cases (Group A vs. B, respectively), as the patients were unexpectedly in cardiac arrest on the arrival
Table 14: Drug etiology of cardiac arrest when resuscitation attempted. Group A (cardiac arrest caused by heroin overdose) and group B (cardiac arrest caused by acute drug poisoning by agents other than heroin). Cardiac arrest patients treated by Helsinki Emergency Medical Service from 1.1.1997 to 31.12.2000 (Study II).

**Drug etiology in group A**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin only</td>
<td>3</td>
<td>16%</td>
</tr>
<tr>
<td>Concomitant use of ethanol or/and benzodiazepines</td>
<td>8</td>
<td>42%</td>
</tr>
<tr>
<td>Traces of other drugs found</td>
<td>8</td>
<td>42%</td>
</tr>
<tr>
<td>Amphetamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Drug etiology in group B**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>24</td>
<td>45%</td>
</tr>
<tr>
<td>Psychotropic drugs</td>
<td>20</td>
<td>38%</td>
</tr>
<tr>
<td>Opioids (other than heroin)</td>
<td>5</td>
<td>9%</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1</td>
<td>2%</td>
</tr>
</tbody>
</table>

of the first responding unit (Table 15). All patients in both groups had asystole or a pulseless rhythm (PEA) as an initial rhythm (Table 15), except for a case of ventricular fibrillation (VF) in a patient suffering from amitriptyline poisoning (Study II: Table 4). Arrival on scene and return of spontaneous circulation (ROSC) time intervals were similar in both groups (Table 16). Admission and discharge rates are presented in Table 15.

In group A, three patients survived to discharge (Study II: Table 4). One had an EMS witnessed arrest, another called the emergency dispatching centre himself and collapsed after that and, in the third case, the emergency call was made immediately after the patient suffered respiratory arrest. In addition to epinephrine (Study II: Table 4), all patients received bag-mask ventilation and chest compressions. None of the patients who received bystander CPR survived.

In group B, six patients survived to discharge (Study II: Table 4). Two had a bystander and four an EMS witnessed arrest. One of the bystander witnessed arrest patients received bystander CPR (mouth-to-mouth ventilation only). He had asystole as primary rhythm and was administered up to 5 mg of epinephrine in addition to basic CPR before attaining ROSC. One patient was in VF and attained ROSC after defibrillation. Another patient, with asystole as the initial rhythm, attained ROSC after bag-mask ventilation and chest compression alone. All other patients were administered epinephrine 2-6 mg in addition to basic CPR before ROSC was attained.
Survivors in both groups suffered from rhabdomyolysis and acute renal failure, hypothermia and/or hypoglycemia.

**Table 15:** Characteristics and comparison of group A (cardiac arrest caused by heroin overdose) and group B (cardiac arrest caused by acute drug poisoning by agents other than heroin). Resuscitation attempted. Cardiac arrest patients treated by Helsinki Emergency Medical Service from 1.1.1997 to 31.12.2000 (Study II).

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=19)</td>
<td>(n=53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)$^1$</td>
<td>29 (22;35)</td>
<td>44 (35;52)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>18 (94.7)</td>
<td>36 (67.9)</td>
<td>0.029</td>
</tr>
<tr>
<td>Scene of collapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private residence, n (%)</td>
<td>12 (63.2)</td>
<td>39 (73.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Public indoors, n (%)</td>
<td>6 (31.6)</td>
<td>2 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Public outdoors, n (%)</td>
<td>1 (5.3)</td>
<td>11 (20.8)</td>
<td></td>
</tr>
<tr>
<td>Ambulance, n (%)</td>
<td>0</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Witnessed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>10 (52.6)</td>
<td>31 (58.5)</td>
<td>0.547</td>
</tr>
<tr>
<td>EMS witnessed, n (%)</td>
<td>1 (5.3)</td>
<td>6 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Bystander CPR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>6 (31.6)</td>
<td>14 (26.4)</td>
<td>0.773</td>
</tr>
<tr>
<td>Collapse to call delay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate, n (%)</td>
<td>1 (5.3)</td>
<td>8 (15.1)</td>
<td>0.111</td>
</tr>
<tr>
<td>Short, n (%)</td>
<td>7 (36.8)</td>
<td>17 (32.1)</td>
<td></td>
</tr>
<tr>
<td>Medium, n (%)</td>
<td>6 (31.6)</td>
<td>5 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Long, n (%)</td>
<td>4 (21.1)</td>
<td>17 (32.1)</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest not Recognized$^2$, n (%)</td>
<td>6 (31.6)</td>
<td>21 (39.6)</td>
<td>0.592</td>
</tr>
<tr>
<td>MICU present, n (%)</td>
<td>17 (89.5)</td>
<td>49 (92.5)</td>
<td>0.651</td>
</tr>
<tr>
<td>Initial rhythm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VF</td>
<td>0</td>
<td>1 (1.9)</td>
<td>0.413</td>
</tr>
<tr>
<td>Asystole</td>
<td>17 (89.5)</td>
<td>41 (77.4)</td>
<td></td>
</tr>
<tr>
<td>PEA</td>
<td>2 (10.5)</td>
<td>11 (20.8)</td>
<td></td>
</tr>
<tr>
<td>Admitted</td>
<td>10 (52.6)</td>
<td>22 (41.5)</td>
<td>0.432</td>
</tr>
<tr>
<td>Discharged alive</td>
<td>3 (15.8)</td>
<td>6 (11.3)</td>
<td>0.690</td>
</tr>
</tbody>
</table>

EMS= Emergency Medical Service; CPR= cardiopulmonary resuscitation; MICU= mobile intensive care unit; VF=ventricular fibrillation; PEA= pulseless electrical activity.
1) Median values (25 and 75 percentiles in parentheses).
2) Cardiac arrest not recognized by emergency dispatching centre.
Table 16: Comparison of time intervals between group A (cardiac arrest caused by heroin overdose) and group B (cardiac arrest caused by acute drug poisoning by agents other than heroin). Cardiac arrest patients treated by Helsinki Emergency Medical Service from 1.1.1997 to 31.12.2000 (Study II).

<table>
<thead>
<tr>
<th>Time intervals (seconds)</th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Call to dispatching (FR)</td>
<td>81.0 (71.3;95.8)</td>
<td>69.0 (49.0;121.5)</td>
<td>0.496</td>
</tr>
<tr>
<td>Call to dispatching (MICU)</td>
<td>82.5 (75.8;120.5)</td>
<td>131.0 (69.5;274.5)</td>
<td>0.284</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time intervals (minutes)</th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Call to arrival on scene (FR)</td>
<td>8.0 (7.0;10.3)</td>
<td>9.5 (7.5;11.0)</td>
<td>0.269</td>
</tr>
<tr>
<td>Call to arrival on scene (MICU)</td>
<td>11.5 (8.0;15.3)</td>
<td>15.0 (11.0;19.0)</td>
<td>0.109</td>
</tr>
<tr>
<td>Call to ROSC</td>
<td>18.5 (16.8;22.3)</td>
<td>25.0 (15.5;29.0)</td>
<td>0.281</td>
</tr>
</tbody>
</table>

1) Median values (25 and 75 percentiles in parentheses).
FR= first responding unit; MICU= mobile intensive care unit; ROSC= return of spontaneous circulation.

Cardiovascular changes after naloxone administration in propofol-sedated piglets during opioid overdose (IV)

Eight unpremedicated piglets were used for the experiment. Four of them had to be given naloxone before the end of the ten minute time point (after morphine administration) due to severe hypoxemia and imminent cardiac arrest. In these subjects the 11-, 15- and 20-minutes time points (i.e. 1-, 5- and 10-minutes post naloxone administration) were calculated from this point onwards. Two of these piglets went into cardiac arrest (VF and PEA) at 4 and 2 minutes after naloxone administration, respectively.

Morphine administration resulted in a marked respiratory depression, which was reversed by naloxone (Study IV: Table 1). There was a statistically significant increase in the mean arterial pressure (MAP) immediately after naloxone administration: from 81 (49-90) mmHg at the ten minutes time point versus 136 (118 -156) mmHg at 11 minutes (P=0.043) (Study IV: Fig. 2). With the exception of the two animals mentioned previously, the administration of naloxone did not provoke arrhythmias, cardiac ischemia or visible evidence of pulmonary edema. No statistically significant differences in MPAP or the ejection fraction were found during the experiment (Study IV: Fig. 2 and 3).

Norepinephrine levels increased before naloxone administration (median, 25 and 75 percentiles parentheses): from 1.9 (1.3-2.3) ng/ml at baseline, to 31.7 (8.3-83.0) ng/ml at the 10-minute time point (p=0.012) (Study IV: Fig. 4). No statistically significant differences were noted when comparing the baseline and the 20-minute time point levels, as the catecholamine levels continued to increase in only one of the animals after naloxone administration (Study IV: Fig. 4 and 5).
DISCUSSION

Incidence of opioid overdose treated by Helsinki EMS in 1995-2007 (unpublished data)

Incidence of all presumed opioid overdose
There was a remarkable decline in opioid, especially heroin, related overdoses treated by Helsinki EMS since the beginning of the millenium. In 2004, only six presumed opioid and no heroin related overdose patients were encountered. This was followed by an increase to 25 presumed opioid overdose patients treated in 2005 (Fig. 2, unpublished data). The low incidence of heroin overdose is also reflected in the disposition of presumed opioid overdose patients after prehospital care. Overdoses caused by other opioids than heroin are more likely to be transported to an ED (Fig. 5, unpublished data). In the beginning of the study period, however, the majority of the opioid overdose patients were transported due to the novelty of heroin overdose: the number of patients has been stable since (Helsinki EMS treated 24 and 26 non-fatal presumed opioid overdoses in 2006 and 2007, respectively). Fatal heroin/morphine related overdoses also declined after 2000 in Finland. Heroin overdose was considered to be the cause of death for 50 cases in 1999 (Vuori et al. 2001). From 2000 to 2004 it was considered to be the cause of death in 60, 25, 4, 4 and 0 cases, respectively (Vuori et al. 2006).

Similar changes in heroin overdoses have been reported in Australia (Degenhardt et al. 2005) and Canada (Wood et al. 2006) during the same time period. In Australia, both fatal and non-fatal heroin overdoses decreased by 40-85%, and the number of clean needles distributed declined at least in the states of New South Wales and Victoria (Degenhardt et al. 2005). In Canada, when comparing 1998-2000 and 2001-2003 data, a decline was seen for annual overdose mortality (35% reduced), naloxone use (45% reduced) and kilograms of heroin seized (64% reduced) (Wood et al. 2006). Although the majority of heroin in both Australia and Canada is supplied by the same source, South-East Asia (Gibson et al. 2005), the reasons behind these changes have been under debate, and might not be similar in both countries (Caulkins & Reuter 2006, Gossop 2005, Smithson 2006, Tyndall 2005).

It seems unlikely that the situation in Finland would be linked to that in Australia or Canada. Contrary to Oceania and North America, heroin used in Western Europe and Finland is mainly derived from opium cultivated in Afghanistan (Gibson et al. 2005). It has been estimated that in 2005 Afghanistan was responsible for producing 88% of the world’s illicit opium (UNODC 2006 I). From 2000 to 2001 the Taliban regime in Afghanistan posed a ban on opium cultivation (Farrell & Thorne 2005) which caused an estimated decrease in potential opium production from over 3000 metric tons in 2000 to under 200 metric tons in 2001 (UNODC 2006 I). The ban seemed to have little or no effect on heroin supply in Europe, however (Gibson et al. 2005). In Finland, the retail (street) price of heroin actually decreased from 250 US$/g in 1999 to 121 US$/g in 2001 (UNODC 2006 II).
Incidence of buprenorphine overdose

The relative incidence of buprenorphine overdoses treated by the Helsinki EMS increased during the study period (Fig. 2, unpublished data). Similar findings concurring with increasing buprenorphine abuse were made in other studies and buprenorphine was increasingly found in the toxicological samples of overdose victims. From 2000 to 2004 the number of fatal buprenorphine overdose cases increased from 3 to 36 (Vuori et al. 2006). Buprenorphine was found in a large number of toxicological samples in 2003 (73 deceased) and 2007 (97 deceased); however, the number of cases in this time frame where it was considered to be the most important finding in an overdose death remained more or less constant, between 28-35 cases annually (Vuori et al. 2009). These findings implicate that although the use of buprenorphine has increased, the relative incidence of fatal buprenorphine overdoses has not increased.

In a study by Partanen et al. in three big cities in Finland (Helsinki, Turku and Tampere) from 2000 to 2003, nearly 66% of the injecting drug users in the study had used amphetamine, 59% buprenorphine and 33% heroin in the previous 30 days. When asked about drugs used on a daily basis, however, 33% had injected buprenorphine, 17% amphetamine and 13% heroin. In 2001, 12% of drug abusers seeking treatment were addicted to buprenorphine and 13% to heroin. In 2002, the respective figures were 20% and 6%. Only 6% reported starting injecting drugs with buprenorphine (Partanen et al. 2004). Thus, the traditional division of drug users between amphetamine versus opioid users appears to have changed. In a study by Malin et al., buprenorphine was reportedly used as a method of self-treatment, not as a drug-of-abuse per se, even when injected. Of the twelve persons interviewed in the study, five reported having used buprenorphine to wean themselves from heroin and four from amphetamine (Malin et al. 2006).

In Glasgow, an opposite trend was noted in the early half of the 1990’s as drug-related deaths increased from 10-15 to 101 per year. The increased death rate was thought to have been caused by drug users moving from injecting a buprenorphine and temazepam combination to the use of heroin, benzodiazepines and alcohol. The changes in injecting habits were thought to be caused by the banning of the prescription of buprenorphine and changing the formulation of temazepam to a less easily injectable form. During the same time-period, however, also the availability and quality of heroin increased in the region (Hammersley et al. 1995). After introduction of high dose buprenorphine (Subutex®) for drug replacement therapy in France in 1996, the number of fatal heroin overdoses have decreased from 500 cases per year to less than 100 per year in 1999 (Kintz 2001).
Comparison of buprenorphine and heroin related overdoses treated by Helsinki EMS in 1995-2005 (unpublished data)

The presumed opioid overdose patients in the study were mainly males in their twenties or thirties and over one third of them used other drugs or/alcohol concomitantly during their overdose (Table 4, unpublished data). These findings concur with previous studies on opioid users (Bammer et al. 1995, Bertini et al. 1992, Cook et al. 1998, Osterwalder 1995, Osterwalder 1996, Smith et al. 1992, Watson et al. 1998). The increase in incidence during weekend evenings has also been reported previously (Manfredini et al. 1994, Ruttenber & Luke 1984) and is partly due to recreational drug use (Ruttenber & Luke 1984).

Over 85% of heroin overdose patients showed signs of respiratory depression. In comparison, two thirds of the patients claiming to have used buprenorphine and overdosed showed similar signs (Table 5, unpublished data). Although considered to be a safe drug, with which one cannot overdose, many buprenorphine injectors themselves report experiencing overdoses with it (Malin et al. 2006). When intravenous buprenorphine alone was administered to healthy, opioid-naive humans, it caused a decrease in minute ventilation up to 50% of baseline (Dahan et al. 2005, Dahan et al. 2006, van Dorp et al. 2006). There was a ceiling in respiratory depression in the dose range 0.05-0.6 mg (Dahan et al. 2006). Whereas, when buprenorphine was administered i.v. to experienced heroin users, the greatest mean maximum decrease in oxygen saturation from baseline was obtained with an 8 mg dose (maximum decrease in saturation from 99% to 80%). The decreases in oxygen saturation had a duration of a few seconds and resolved after mild auditory stimulation. However, marked individual variability in the degree of respiratory depression was noted in the study (Umbricht et al. 2004). Also, the authors discussed the possibility of a more profound respiratory depression if the participants had been allowed to fall asleep (Umbricht et al. 2004) or if pain testing had not have been a part of the experiment (Dahan et al. 2006).

In the current investigation, 70% of the presumed buprenorphine overdose patients had reportedly used other drugs concomitantly, mainly alcohol and benzodiazepines (Table 5, unpublished data). Polydrug use was probably underreported, as it is exceedingly common in buprenorphine related fatal and non-fatal overdoses (Kintz 2001, Tracqui et al. 1998). Buprenorphine and benzodiazepines are prone to cause respiratory depression even when therapeutic doses are used in postoperative patients (Forrest 1983, Papworth 1983). In rats, buprenorphine or midazolam administered alone caused only mild respiratory depression, while the combination of both administered in similar doses caused a rapid, marked and prolonged respiratory depression with delayed hypoxemia (Gueye et al. 2002 II).

The naloxone doses used to treat the buprenorphine related overdose patients were up to 0.8 mg in the present studies. The literature suggests, however, that respiratory depression caused by buprenorphine requires larger doses of naloxone to be reversed (van Dorp et al. 2006, Gal 1989, Heel et al. 1979). In a study done on healthy volunteers, an intravenous naloxone dose of 0.8 mg had no effect on respiratory depression caused by 0.2 mg of intravenous
buprenorphine, but doses of 2-4 mg of naloxone were required (van Dorp et al. 2006). In comparison to the study done by van Dorp et al., the presumed buprenorphine overdose patients in the current study were not opioid naïve and polydrug use was involved in the majority of cases. As naloxone has also been shown to reverse the effects of alcohol and other central nervous system depressants (Howland & Nelson 2010, Mackenzie 1979, McCauley et al. 1988, Michiels et al. 1983, Sorensen & Mattison 1978), it might have had another role than reversal of opioid toxicity in our patients. Also, not all of the patients responded to naloxone administration, or responded to it very slowly and remained heavily sedated after prehospital care. The latter findings concur with those made by Gal on reversing the effects of buprenorphine with naloxone (Gal 1989).

On one occasion, a patient that succumbed to a heroin overdose was treated by his friends by injecting i.v. crushed buprenorphine tablets (Study I). The fear of police involvement has led addicts to try to manage opioid overdose victims by themselves rather than call for help (Darke et al. 1996 II). Attempting to treat heroin overdose patients by injecting solutions such as saline is not a novel idea (Louria et al. 1967). Crushed naltrexone has also been injected during CPR, after which the patient regained consciousness (Galloway 1993). Following fentanyl anesthesia, buprenorphine was found to be as effective as naloxone in antagonizing ventilatory depression (Boysen et al. 1988). Still, actions like this should not be encouraged. Instead one should stress the importance of calling the emergency dispatching centre and providing bystander CPR without delay. The use of “home remedies” diverts time and attention from these actions and might lead to criminal charges.

Recurrent opioid toxicity after prehospital care of presumed heroin overdose patients (III)

Patients excluded from the study


Recurrent respiratory depression in the ED

Twenty percent of heroin and 35% of opioid and polydrug users had documented recurrent respiratory depression and were administered naloxone in the ED: the majority of these patients had already presented signs of recurrent opioid toxicity prior to arrival at the ED. Three patients with presumed heroin overdose suffered from other complications related to opioid abuse; aspiration of gastric contents, hypothermia and rhabdomyolysis. These would have also been apparent after close examination. In the excluded polydrug users, if signs of opioid toxicity were not apparent on arrival at the ED, the time intervals between prehospital and ED administered naloxone were 100, 104 and 173 minutes. The patient with the longest time interval (173 minutes) reported taking unspecified antidepressant drugs enterally just prior to the use of intravenous heroin. The time intervals were not available in two
cases. In relation to the emergency dispatching centre call time and the median ALS/MICU response time of 12 minutes, the time intervals could have not been more than 60 and 120 minutes.

The duration of naloxone effect depends on the dosage, route of administration and individual metabolic rate of that drug (Chamberlain & Klein 1994, Handal et al. 1983). In addition, the appearance of recurrent respiratory depression depends also on the type of opioid involved, its dose and the route of administration (Chamberlain & Klein 1994, Watson et al. 1998). Accordingly, after the reversal of opioid toxicity with naloxone, the recommended observation times vary from 1-24 hours (Christenson et al. 2000, Nelson & Olsen 2010, Osterwalder 1995, Smith et al. 1992, Sporer 1999).

In an American double-blind, randomized study done in the ED, patients with a suspected opioid overdose were administered 2 mg i.v. naloxone. Naloxone had a duration of effect of at least 240 minutes, similar to 1 and 2 mg of intravenous nalmefene, another opioid antagonist. In all groups tested, at least 60% of the patients had used opioids other than heroin (methadone, codeine, meperidine, oxycodone or propoxyphene) and/or other central nervous system depressants (ethanol, benzodiazepines, tricyclic antidepressants, phenothiazines, barbiturates or glutimide) (Kaplan et al. 1999). At around the same time, a retrospective study was done on ED patients by Watson et al., where a recurrence of opioid toxicity (somnolence or hypoventilation) was seen between 3 and 120 minutes after an initial response to naloxone: the naloxone dose most frequently used was 2.0 mg i.v. The majority of patients that suffered from recurrent toxicity (11/85%) had used oral opioids and only 2 had used heroin. Whilst the concomitant use of other central nervous system depressants had no effect on the recurrence of opioid toxicity, an opioid positive urine drug screen was available for 7 (8%) of the 84 patients in the study, however (Watson et al. 1998). In contrast, in a study by Smith et al., 96 patients with presumed intravenous heroin overdose received 2-6 mg of naloxone either i.m. and/or i.v. in an ED: no recurrence of respiratory depression was observed (Smith et al. 1992). When comparing the previous studies to the present study (III), naloxone doses were higher than used by Helsinki EMS and opioids other than heroin were mainly used in the studies by Kaplan et al. and Watson et al.

An Austrian study of opioid overdose patients treated by EMS and transported to an ED reported that a quarter of the patients (n=19) were administered additional naloxone in the ED, in one case 4 hours after admission (Seidler et al. 1996). A later prospective study on opioid overdose patients that could be mobilized normally, reported a GCS of 15 in addition to a normal respiratory status, heart rate and temperature one hour after naloxone administration; they were considered safe to discharge (Christenson et al. 2000). The majority (68%) of patients was considered to have experienced opioid overdose without polydrug use and because of the availability of inexpensive high-grade heroin, the opioid used was probably heroin (Christenson et al. 2000). The naloxone doses used in the aforementioned studies were similar to those used by Helsinki EMS. In the present study, it is noteworthy that there were seven
patients that made full recovery after naloxone administered by the EMS only to later develop signs of recurrent opioids toxicity in the ED.

The administration of naloxone i.m. or s.c. reduces the incidence of recurrent respiratory depression and seems to prolong the duration of naloxone effect in comparison to only i.v. administration. Only 13% of the patients that were administered naloxone s.c. or i.m. by EMS were also administered naloxone subsequently in the ED. In comparison, over one third of the patients that were administered prehospital naloxone only i.v. were administered naloxone in the ED. The time interval between naloxone administered at the scene and in the ED was also longer when naloxone was administered s.c. or i.m. In a study on postoperative patients, a duration of effect of 6 hours or more has been reported after a combined intravenous and intramuscular naloxone administration: following general anesthesia and a total morphine dose of 1.4 ± 0.04 mg/kg, patients were administered naloxone i.v. and i.m. (5 μg/kg i.v. and 10 μg/kg i.m.) (Longnecker et al. 1973). In comparison, the naloxone doses used by Helsinki EMS were smaller (0.6 and 0.8 mg) and naloxone in the ED was administered 3-4 h after prehospital naloxone. The sample size, however, was small (two patients) and one of them already had signs of recurring opioid toxicity already 30 minutes after prehospitaly administered naloxone. The other patient, a 15-year old boy, had a peripheral oxygen saturation of 95% on arrival at the ED, an abnormal value for a previously healthy youth.

Patients allowed to sign out after prehospital treatment
In the present study, none of the patients treated with prehospital naloxone suffered from severe recurrent respiratory depression due to the same overdose. As drug users are reluctant to seek help (Darke et al. 1996 II), less severe respiratory depression or other complications related to non-fatal overdoses could have occurred, however. An unrecognized non-fatal complication, such as small aspiration pneumonia, could contribute to a fatal overdose in the future (Warner-Smith M et al. 2001). Vilke et al. reviewed heroin overdose patients that were administered naloxone by paramedics and refused further care during a 5-year period from 1996 to 2000 in San Diego, USA. During this time period, the San Diego EMS treated 998 heroin overdose patients that were applicable to the study. The data of these patients were compared to the data of the 601 fatal opioid overdose victims. The majority (552) of patients were administered two doses of naloxone (2+2mg), first i.v. and then i.m. Twenty four patients were administered three doses of naloxone (2+2+2mg). After the patients were revived and refused further care, the paramedics referred to the county protocol for allowing patients to sign out against medical advice and left the patients on the scene. There was no evidence that any of the patients that were treated by the EMS died of an opioid overdose during a 12 hour period after the paramedics left the patient (Vilke et al. 2003). In comparison, the present study not only compared signed out patients to those who died of opioid overdose, but also looked at the patients successfully resuscitated from cardiac arrest and those requiring a revisit by an ambulance. The naloxone doses used in the current study were lower than those used by Vilke et al. As all urgent ambulance calls are managed and also out-of-hospital deaths are registered by Helsinki EMS, it is most unlikely that the system would have been unaware of an adverse
outcome in patients that were administered prehospital naloxone and left on the scene. One patient was found dead after refusing further care and being left on scene, but he was not administered naloxone by the EMS.

Adverse effects related to naloxone use
Potentially adverse effects due to naloxone, such as vomiting and aggressive behaviour, were recorded in few patients in the present study (unpublished data). Similar adverse effects, probably due to acute opioid withdrawal or hypoxemia suffered during the overdose, have been reported previously with an incidence of 0.6-16% (Kaplan et al. 1999, Yealy et al. 1990). More serious adverse events, such as arrhythmias (Michaelis et al. 1974), cardiac arrest (Andree 1980), pulmonary edema (Osterwalder 1996, Smith et al. 1992) and convulsions (Bujard et al. 2004, Yealy et al. 1990) have also been reported previously. Pulmonary edema has been reported with naloxone doses from 0.2 to 0.5 mg (Prough et al. 1984, Taff 1983, Wride et al. 1989), even as low as 80 μg (Johnson et al. 1995, Partridge & Ward 1986). As such, pulmonary edema has been reported after heroin overdose, in the absence of naloxone (Duberstein & Kaufman 1971). Underlying chronic cardiac or pulmonary diseases, various medications administered during general anesthesia, sudden severe pain caused by the reversal of analgesia or the unmasking of acute lung injury caused by drug abuse or idiosyncratic reactions might also be involved (Chamberlain & Klein 1994, Nelson & Olsen 2010). In the present study the median dose of naloxone was 0.4 mg and the range was 0.04-1.6 mg. In contrast to some previously mentioned studies, no severe adverse effects were recorded.

GHB/GBL overdoses involving injecting drug users in Helsinki (V)
About half of the GHB/GBL overdoses occurred during weekends and/or from midnight to 4 a.m. (Fig. 7 and 8) in this study. This is probably related to the role of GHB/GBL as recreational drugs (Dietze et al. 2008, Snead et Gibson 2005, West et al. 2008). Similar findings have also been made in previous studies (Miro et al. 2002, Wood et al. 2008). Similar findings have been previously made with heroin overdose patients both in other countries and in Helsinki (Boyd unpublished data, Manfredini et al. 1994, Ruttenber & Luke 1984). Patients were predominately encountered in areas where the night life is concentrated (city centre and Kallio) or where substance abuse is popular (Kallio).

According to the present study, there appears to be at least two distinct groups of GHB/GBL users. Patients overdosing with GHB/GBL and alcohol on weekend nights in indoor public places (group C) and patients with chronic injecting drug use overdosing with GHB/GBL in the middle of the week or early evenings on the weekend in private residences or outdoors (group D) (Tables 11 and 13). When comparing GHB and heroin overdose patients, a similarity in the relative locations of overdoses has been noted previously (Dietze et al. 2008). To the knowledge of the author, the incidence of GHB/GBL overdoses involving chronic injecting drug users has not been previously reported. As both GHB and GBL are relatively easy to obtain, cheap (a 50 ml bottle costs 5-6 €) (Boyd, unpublished data) and highly addictive (Snead & Gibson 2005), it is easy to see the potential of it as a drug of abuse also among injecting drug users.
Polysubstance use is common with GHB use (Li et al. 1998 I, Miro et al. 2002, Snead & Gibson 2005, West et al. 2008, Wood et al. 2008). Other central nervous system depressants, namely ethanol, may have a synergistic effect with GHB (Mason & Kerns 2002, Snead & Gibson 2005). However, in one study, the concomitant use of ethanol and GHB was rather related to aggressive behavior, which is sometimes seen during GHB related intoxications (Liechti et al. 2006). Polydrug use, as such, was less often reported in group D (Table 12). This could be due to the concomitant use of other, more illegal substances, by injecting drug users and thus unwillingness to report them. Although there were no statistically significant differences, flumazenil and naloxone were administered more often in group D (Table 11), although, naloxone did not appear to have any effect. In group C, flumazenil was administered to six patients: a GCS of 6 was recorded in four of them, while the other two were recorded to be either “unconscious” or “unresponsive to pain”. After flumazenil administration, the GCS had increased in the four patients to 8, 9, 11 and 13. In group D, flumazenil was administered to five patients. Only two of them were recorded to have an increase of GCS from five to 13 and 14. In group D, one patient was also administered both naloxone and flumazenil without any response.

**Mechanism of respiratory depression in overdose patients (III, V)**

As the roles of different drugs, medicines and alcohol in the overdose patients of the current study are unclear, so is the mechanism of respiratory depression. Heroin and other opioids depress the respiratory centre and thus cause hypoventilation and hypoxemia (Gutstein & Akil 2001). Alcohol and other central nervous system depressants primarily cause a reduced level of consciousness and an upper airway obstruction leading to hypoventilation (Gueye et al. 2002 I). Aspiration of gastric content or a foreign body can also lead to hypoxemia (Stolbach & Hoffmann 2010, Warner-Smith et al. 2001). As the positioning of the patients was rarely, if ever, recorded in the EMS records, it is impossible to say if upper airway obstruction contributed to the respiratory depression of the patients.

**Outcome after heroin overdose and cardiopulmonary resuscitation (II)**

The heroin overdose patients that suffered from cardiac arrest and were resuscitated were almost solely (94.7%) male and in their late twenties or early thirties. These results are consistent with previous studies on heroin overdose deaths (Darke et al. 2000, Darke & Zador 1996, Gossop et al. 2002, Preti et al. 2002, Sheedy et al. 2003). The most common scene of collapse in the heroin overdose group was an indoor location. Similar findings have also been made in previous studies on heroin overdose patients and could be due to an attempt to conceal drug use (Darke et al. 1996 I, Darke et al. 2000). Over 60% of the patients did not receive any bystander CPR. As the majority of heroin overdose deaths occur in the presence of others (Darke & Zador 1996, Powis et al. 1999), there could be a chance to improve survival by peer education and possibly by making naloxone available at home (Darke & Hall 2003, Sporer 2003, Sporer & Kral 2007, Strang 2006).

Death was caused by multidrug or ethanol use in the majority of the heroin overdose patients (Table 14). There is an increasing trend of concomitant use of other drugs, especially ethanol and benzodiazepines in fatal heroin
overdoses (Darke et al. 2000, Darke & Zador 1996, Gossop et al. 2002, Preti et al. 2002, Ruttenber & Luke 1984, Sheedy et al. 2003). In a recent study by Sheedy et al. (Sheedy et al. 2003), heroin was used alone in only 17% of the cases. The concomitant use of other central nervous system depressants increase the effect of heroin on respiration (White & Irvine 1999). Genetic predisposition (White & Irvine 1999) and co-existing pulmonary and hepatic diseases might also increase the possibility of a severe heroin overdose (Warner-Smith et al. 2002).

The survival rate of all of the acute drug poisoning patients with cardiac arrest in the present study, 9/72 (12.5%), was similar to that of Paredes et al. 11/85 (12.9%) (Paredes et al. 2004). In the present investigation, all except one patient had an initial rhythm that was either asystole or PEA (Table 15). In general, survival after asystole is poor (0.2-0.8%) (Stiell et al. 2004) and survival after PEA only slightly better (1.8%) (Kuism & Alaspää 1997) in comparison to survival after bystander witnessed VF of a cardiac cause (32.5%) (Kuism & Määttä 1996).

Resuscitation was attempted in 19 heroin overdose patients. Three patients survived to discharge, two with overall performance category (OPC) 1 or 2 and one with OPC 3. Survival after heroin overdose leading to cardiac arrest is virtually nonexistent (Smith et al. 1992, Sporer et al. 1996), with some exceptions (Bertini et al. 1992, Skulberg et al. 1993). In an Italian study (Bertini et al. 1992), the survival rate was outstanding (57%), but the definition of cardiac arrest has been questioned (Sporer et al. 1996). In a study done in Oslo by Skulberg et al., of 19 heroin overdose patients with asystole as their initial rhythm, 13 (68.4%) patients recovered without sequelae. Spontaneous circulation was achieved by five of the patients with ventilation and chest compression alone and by eight patients with epinephrine. One patient achieved ROSC, but died before reaching hospital, whilst five patients were unresponsive to resuscitation efforts (Skulberg et al. 1993). In a study done in Copenhagen (Ishoy et al. 2003), resuscitation was attempted in 22 heroin overdose patients in cardiac arrest; four (18%) patients attained ROSC. Again, these survival rates seem high in comparison to other studies referred to previously. In the study by Paredes et al. (vide supra), 11 patients with cardiac arrest caused by acute drug poisoning were successfully resuscitated. ROSC was achieved by EMS provided bag-valve-mask ventilation and chest compressions alone in six patients. The remaining patients required defibrillation (n=1) or additional advanced life support measures (n=4) before ROSC was attained (Paredes et al. 2004). It is possible that the good survival rates presented in some of these studies is due to the patients being in only respiratory arrest and severe bradycardia or their pulse was impalpable, that is to say that they were not in true cardiac arrest. The fact that some of the patients attained ROSC with ventilation and chest compression alone would seem to support this (De Maio et al. 2001). In the present study, the survivors of heroin overdose leading to cardiac arrest required a total dose of 2-10 mg of epinephrine and 12-20 minutes of ventilation and chest compressions before achieving spontaneous circulation (Study II: Table 4). Thus, it seems unlikely that they would not have been in true cardiac arrest.
In Helsinki, dispatcher assisted CPR instructions are provided for callers without prior CPR training. The instructions for adult cardiac arrest patients include chest compressions only (Hallstrom et al. 2000). Instructions for both mouth-to-mouth ventilation and chest compressions are given when treating near-drowning and suffocation victims. Hypoventilation is the most probable mechanism of death in opioid overdoses (Gutstein & Akill 2001) and in other intoxications caused by central nervous system depressing agents (Gueye et al. 2002 I, Heard & Paradis 2007). Although none of the heroin overdose patients in cardiac arrest that received bystander CPR survived in the present study, this may be attributed to poor ventilation thus instructions for mouth-to-mouth ventilation should be included in this group of patients also (Dietze et al. 2002).

After an acute drug poisoning leading to cardiac arrest and successful resuscitation, low blood glucose levels were measured using capillary blood in four patients, two prehospitaly and two in the ED (Study II: Table 4). Hyperglycemia, rather than hypoglycemia, is a common finding in acutely ill adult patients (Foo et al. 2003, Inamasu et al. 2002, Seidler et al. 1996, Van den Berghe et al. 2001) and in patients resuscitated from cardiac arrest (Calle et al. 1989, Longstreth et al. 1983, Longstreth & Inui 1984, So et al. 1994). In contrast, hypoglycemia is common in acutely ill pediatric patients, including intoxications. In a prospective study by Losek, 18% of nontrauma children were hypoglycemic (Losek 2000). Liver disease and sepsis have also been reported as a cause of hypoglycemia in ED population (Su 2006).

Opioids have been shown to induce mild hyperglycemia in man. This has been thought to be a result of both central activation of adrenal catecholamine secretion (Feldberg & Shaligram 1972) and peripheral opioid receptors (Ipp et al. 1980, Paolillo et al. 1987). In mice, s.c. administered morphine produces a dose-depandant hyperglycemia that is antagonized by naloxone (Lux et al. 1988), however blood glucose levels during or after an opioid overdose are not discussed in literature. In a study done on ED patients being evaluated for ethanol intoxication, ethanol and glucose concentrations showed no correlation. The five (0.9%) patients that had detectable ethanol concentrations and were hypoglycemic had several visits to the ED due to ethanol intoxications (Sucov & Woolard 1995). To the author’s knowledge, none of the patients in the present study had used insulin or oral hypoglycemic drugs. All the patients that presented low blood glucose measurements had received 5-10 mg of adrenaline during resuscitation (Study II: Table 4), however adrenaline should increase blood glucose levels via its action on -adrenoreceptors (Hoffman 2001). Overall, the mechanism of hypoglycemia in these cases is unclear.

In healthy volunteers, capillary blood glucose values best approximated with venous plasma glucose values from the laboratory. Using venous blood with a glucometer that is intended to use capillary blood, however, resulted in an overestimation of blood glucose levels by almost 1 mmol/l in comparison to laboratory results (Kumar et al. 2004). In patients with poor peripheral circulation capillary blood glucose levels can be inaccurately low in comparison to laboratory results using blood serum glucose. In a prospective trial consisting of 50 patients receiving CPR, only 3 out of 8 patients identified
to be hypoglycemic (<3.8 mmol/l) by capillary blood analysis were truly hypoglycemic. Two of the patients were actually hyperglycemic (Thomas et al. 1994). In a prospective trial comparing 25 hypotensive (systolic blood pressure 80 mmHg or less) and 39 normotensive patients, 36% of the hypotensive patients had capillary blood glucose values within 20% of the laboratory blood glucose values in comparison to 90% of the normotensive patients. Out of ten patients deemed hypoglycemic by capillary blood glucose levels in the hypotensive group, only 2 were truly hypoglycemic (Atkin et al. 1991). In the present study, the blood samples were taken after achieving spontaneous circulation and the patients that had low blood glucose levels did not suffer from marked hypotension. Normal or even high blood pressure does not ensure good peripheral circulation, however (Peters et al. 2001). Two patients that survived to discharge suffered from severe hypotension (systolic blood pressure < 80 mmHg) after ROSC. They had normal or high blood glucose levels when measured (Study II: Table 4).

Complications related to opioid overdose (II, III)

Among the patients transported to an ED, 16% reportedly suffered from complications other than recurrent respiratory depression (Table 8, unpublished data), mainly aspiration pneumonia, aggressiveness and rhabdomyolysis. The reported incidence of morbidity suffered after a non-fatal opioid overdose could be as high as 79% (Warner-Smith et al. 2002) (Table 3). After acute drug poisoning and cardiac arrest, five of the nine survivors suffered from rhabdomyolysis leading to acute renal failure, hypoglycemia and/or hypothermia (Study II: Table 4).

Rhabdomyolysis as a complication of heroin or ethanol overdose is not uncommon. In a study on rhabdomyosis in a civilian population in peacetime, ethanol and drug abuse were responsible for 82% of the cases (Gabow et al. 1982). Usually rhabdomyosis results from the patient being unconscious and remaining motionless for several hours after an overdose. Factors such as hypoxemia, acidosis, hypovolemia and hypothermia may worsen the situation (Henry 2000). Other mechanisms may also exist, such as toxic or immunologic reactions to heroin’s adulterants (Curry et al. 1989). Acute skeletal muscle necrosis with generalized muscle swelling has occurred after heroin used i.v. (Richter et al. 1971) or intranasally (D’Agostino & Arnett 1979). Cardiac muscle damage has also been reported (Schwartzfarb et al. 1997). Ethanol may also cause skeletal muscle damage ranging from slight elevation of serum creatine kinase activity to massive muscle necrosis. Several mechanisms have been proposed, such as inhibition of accumulation of calcium by the sarcoplasmic reticulum, disruption of muscle cell membranes, inhibition of Na-K-ATPase and alteration of muscle carbohydrate metabolism. Hypotension or hypoxemia due to cardiac arrest might also be the cause of rhabdomyolysis (Curry et al. 1989).

Hypothermia (core temperature < 35°C) was recorded in the prehospital phase or on the arrival at the ED in three of the survivors (Study II: Table 4). Several agents, including ethanol and opioids, can cause hypothermia in poisoned patients (Hack & Hoffman 2004). Hypothermia has been reported previously in patients with cardiac arrest due to other reasons than drug overdose (Bernard et al. 2002). Mild to moderate (32 – 34°C) therapeutic
hypothermia appears to improve neurologic outcome in other cardiac arrest patients (Bernard et al. 2002, HACA 2002).

**Cardiovascular changes after naloxone administration in propofol-sedated piglets during opioid overdose (IV)**

In the animal study, morphine and propofol administration caused marked hypoventilation that led to severe hypoxemia and hypercapnia with a concomitant increase in the circulating norepinephrine levels. The median values of circulating catecholamines returned to baseline after naloxone administration, however. There were no statistically significant differences in the MPAP or the ejection fraction during the experiment, possibly due to the influence of the modulating effect of the propofol-infusion (see limitations, *vide infra*). In this study, naloxone did not appear to have any consistent untoward cardiac effects in hypoxemic and hypercarbic subjects during an opioid overdose.

In previous studies by Bossone & Hannon, the intravenous administration of morphine 1 mg/kg to conscious pigs caused an excitatory state, characterized by hyperdynamic circulation, decrease in PaO2 and increase in PaCO2 despite increased ventilation and metabolic acidosis (Hannon & Bossone 1991). Increases in lactate, epinephrine and norepinephrine plasma concentrations were also observed (Bossone & Hannon 1991). However, in a study on the suitability of swine for studying the effects of morphine, the excitation observed did not appear to cause any untoward effects and was attenuated compared to other species that are excited by morphine according to the authors (Risdahl et al. 1992). Hypercapnia and hypoxemia induced during a naloxone infusion caused similar changes in mean arterial pressure, heart rate and cardiac output when compared to 5% dextrose in water infusion in a study where endogenous opioids were antagonized in conscious dogs. The rise in circulating catecholamine levels was enhanced during naloxone infusion, however (Rose et al. 1988). Although hypoxemia was more severe and plasma catecholamine levels were higher in the present study, similar cardiovascular changes to those seen in the study by Hannon & Bossone were not observed. In this study, combined respiratory and metabolic acidosis with lactatemia was observed only in the piglet whose catecholamine levels were continuously rising.

Naloxone may have contributed to the development of VF in one of the animals in the present study. However, immediately before the animal received naloxone, the arterial blood gas values and ejection fraction measured were close to the median values of that time point. Also, the heart rate and blood pressure transiently improved before cardiac arrest occurred. One animal went into PEA after naloxone administration, most probably due to hypoxemia. The arterial blood gas values and ejection fraction of this animal were the most seriously effected in comparison to the other subjects after morphine administration and immediately before naloxone administration. Also, the cardiac arrest occurred as a clear continuum of the relentlessly moribund state that caused naloxone to be administered prematurely.
LIMITATIONS OF THE STUDY

Patient selection and temporal distribution of overdoses
The patients in the studies presented here do not represent all of the patients with drug related overdoses or drug related problems treated by the Helsinki EMS during the study period. Probably both non severe cases and some of the unconscious patients were overlooked due to the lack of knowledge of drug involvement. Also, i.v. drug users are unlikely to call for help when an overdose occurs (Darke et al. 1996 II). When considering the temporal distribution of overdoses, it should be noted that festivities (such as New Years Eve, Christmas, 1st of May and Midsummer) were not considered.

Transported versus non-transported patients in 1995-2000
Over half of the presumed opioid overdose patients (n=163) were transported to an ED after prehospital care from 1.1.1995 to 31.12.2000. This group was neither homogenous nor comparable to the group of patients left on the scene (n=102), however. During the early part of the study period, the majority of opioid overdose patients were transported to an ED. This was partly due to the novelty of these patients. Later on, more and more patients were allowed to sign out after prehospital care and only those who did not recover with prehospital care or were suspected of marked polydrug use were transported.

Toxicological evidence
The most critical limitation of the present study is the lack of toxicological confirmation of the substances used by the patients. This is important especially when considering the differences between heroin and buprenorphine overdoses. Furthermore, confirmation of GHB/GBL use and concomitantly used other substances in GHB/GBL related overdoses would have been valuable. Data on which drugs were used was obtained from the patients after their recovery or from associates or relatives present at the time. For GHB/GBL overdoses, clinical suspicion or obvious signs of drug paraphernalia was only used as a criteria for inclusion in a minority of cases. Even if the patients were transported to an ED, blood samples to confirm the causative agents were taken only rarely. Alcohol breath analyzers were routinely used, however. It is possible that the patients or other people present at the scene preferentially reported buprenorphine rather than heroin use, the latter having been always an illegal substance in Finland. Users might also deny heroin use because of the stigma related to it. Thus, there remains uncertainty regarding which drugs were involved, and if they were indeed involved, what their role was in the overdose. Nonetheless, most other studies on non-fatal opioid/heroine overdose patients share this same problem (Bertini et al. 1992, Buajordet et al. 2004, Christenson et al. 2000, Cook et al. 1998, Osterwalder 1995, Osterwalder 1996, Smith et al. 1992, Sporer et al. 1996, Vilke et al. 2003, Wanger et al. 1998, Watson et al. 1998, Yealy et al. 1990). Toxicological results were available for fatal cases. Furthermore, the recognition of a GHB overdose by clinical signs and symptoms has been previously shown to be reliable (West et al. 2008).
Time intervals
When considering the time intervals between prehospital and inhospital naloxone administration, the exact time when naloxone was given was not recorded for 23 cases in the study (III). The ALS/MICU on scene time was used instead. In the 15 cases where both the ALS/MICU on scene and prehospital naloxone administration times were recorded, the median time interval from arrival of the unit to drug administration was 7 min with a range of 1-23 min. What was not recorded in the ED, however, was the time at which the first signs of recurrent opioid toxicity were noted.

Cardiovascular changes after naloxone administration in propofol-sedated piglets during opioid overdose.
The limitations of this study included the small sample size and the lack of a control group receiving only naloxone. In comparison to heroin overdose patients, the animals were non-opioid dependent and morphine, not heroin, was used to induce respiratory depression. Continuous propofol anesthesia was used due to ethical reasons and to immobilize the animals to aid the echocardiography study. Propofol and morphine could have had an effect on the outcome of the study, however. Propofol has a depressant effect on the cardiovascular system, mainly caused by reductions in vascular resistance and sympathetic tone (Gelissen et al. 1996, Zheng et al. 2003), and protects the myocardium from injuries caused by ischemia and reperfusion (Kokita et al. 1998). On the other hand, an increase in catecholamine plasma concentrations and marked cardiovascular stimulation after naloxone administration has been demonstrated in opioid dependent patients under propofol anesthesia (Kienbaum et al. 2000). Cardioprotective and antiarrhythmic effects are also exhibited by morphine both via opioid receptors (Xia et al. 2005) and ion channel effects (Hung et al. 1998, Xia et al. 2005). As heroin is metabolized to morphine (Inturrisi et al. 1984), similar effects should also be present after heroin administration.
SUMMARY AND CONCLUSIONS

1. The number of presumed non-fatal opioid overdoses treated by the Emergency Medical Services (EMS) in Helsinki peaked in the year 2000, after which they declined rapidly. Reportedly, the most often used opioid during the study period was heroin. The majority of patients were male in their late twenties or early thirties. There appears to be an increase in incidence of overdose on Friday and Saturday evenings. Once true cardiac arrest occurs after heroin overdose, the prognosis is grim.

2. After heroin, buprenorphine was the opioid most often used in opioid overdose: the incidence of buprenorphine related overdose also increased during the study period. Polydrug use was recorded more often in buprenorphine overdose compared to heroin. However, severe respiratory depression was not recorded as often as with heroin related overdoses.

3. The incidence of γ-hydroxybutyrate (GHB) and γ-butyrolactone (GBL) overdose involving injecting drug users increased from 18 to 31 patient contacts from 2006 to 2007. The majority of patients encountered outside the time frame of weekend nights had a history of injecting drug use.

4. After prehospital naloxone administration, none of the presumed heroin overdose patients left untransported to an emergency department (ED) suffered from fatal recurrent opioid toxicity during a 12 hour period. If transported after prehospital naloxone administration, heroin overdose patients had symptoms and signs of recurrent opioid toxicity within one hour of arrival at the ED.

5. In the experimental animal study, naloxone administered during hypoxemic and hypercarbic conditions in propofol-sedated piglets did not cause changes in ejection fraction or mean pulmonary artery pressure. Also, plasma catecholamine levels returned to baseline in all but one animal after naloxone administration. Two animals developed cardiac arrest after receiving naloxone while hypoxemic and bradycardic. Further studies are necessary to evaluate the effect of naloxone during opioid-induced hypercapnia and hypoxemia in animals addicted to opioids.

CLINICAL IMPLICATIONS

1. One of the reasons for the reduced overall incidence of opioid overdoses encountered by Helsinki EMS could be that previous heroin users started to use other drugs such as buprenorphine. This reflects on the disposition of opioid overdose patients after prehospital care, as there is little evidence on the safety of leaving patients on scene with the exception of those suffering a heroin overdose. During a heroin or
opioid overdose, the emergency medical services should be activated before cardiac arrest occurs if there is to be any hope of survival. Thus, education of drug users and people close to them in recognition of overdose, calling the emergency dispatching centre (112) swiftly and giving bystander CPR is paramount.

2. Although the number of buprenorphine related overdoses increased during the study period, the incidence was mostly lower than that those involving heroin. This could mean that either buprenorphine users do not experience overdoses as often as heroin users, the role of buprenorphine is not similar to that of heroin (i.e. the majority of buprenorphine users use it as self-treatment and not for its euphoric effects) and/or more buprenorphine overdose patients are treated by their associates without ever calling emergency dispatching centre.

3. During a serious overdose, GHB/GBL can cause respiratory depression and a reduced level of consciousness, similar to opioids. A GHB/GBL overdose patient encountered during weekdays is more likely to have a history of chronic injecting drug use with all the related problems. The possibility of a GHB/GBL overdose should be also kept in mind when treating injecting drug users with a reduced level of consciousness and respiratory depression, even when evidence of currently administered injectable substances is present.

4. In this study population, it appears to be safe to let heroin overdose patients sign out after prehospital care with naloxone. Part of the total naloxone dose, preferably at least 0.4 mg, should be administered s.c. or i.m. to reduce the risk of recurrent respiratory depression. If transported to an ED, an observation period of one to two hours after the last naloxone dose seems adequate. If no signs of recurrent opioid toxicity have appeared, the patient may be discharged, if required. These findings are not applicable, however, to overdoses caused by opioids other than heroin. The treating clinician must also be vigilant due to the high prevalence of polydrug use and high morbidity after non fatal heroin overdose. It should be pointed out that a one to two hour observation period is due to the fear of recurrent respiratory depression. In addition, the patient’s possible chronic somatic and psychiatric disorders might require further attention. Furthermore, the possibility of drug rehabilitation should at least be discussed with the patient.

5. In conjunction with the retrospective study (III) on prehospital naloxone administered to opioid overdose patients, naloxone does not seem to consistantly cause severe cardiopulmonary adverse effects when administered during opioid overdose.
CURRENT STATUS AND FUTURE ASPECTS

After 2007, buprenorphine surpassed heroin as the principal cause of non-fatal opioid overdose treated by the Helsinki EMS (unpublished data, Helsinki EMS records). The nonmedical use of other licit drugs, including opioids, has also increased (Tammi et al. 2011, Vuori et al. 2009). The traditional division of injecting drug users to amphetamine and heroin users in Helsinki might have changed to widespread polydrug use including opioid analgesics, benzodiazepines and alcohol (Tammi et al. 2011). Internationally, the abuse of licit opioids has also increased. For example, in the USA opioid analgesics caused almost five times more unintentional drug overdose deaths than heroin in 2007 (Okie 2010).

The role of the internet as a drug purchasing venue has also increased (EMCDDA 2010). For example, new designer drugs, such as synthetic cathinones like methylenedioxypyrovalerone (MDPV), 4-methylcathinone (mephedrone) and naphthylyprovalerone (NRG-1), hallucinogenic plants and plant products are available from several websites (EMCDDA 2010, Brandt et al. 2010). Some of them are even portrayed as legal products (“legal highs”) (Ramsey et al. 2010).

Opioid overdoses and their acute care, although important, form only a small part of a larger problem. The ability of the emergency medical services to reduce morbidity and mortality is limited. Enrolment in maintenance treatment has been shown to reduce the risk of overdose (Gronbladh et al. 1990). While the majority of overdose deaths in other countries occur in older, long term users, in Finland and in Sweden the highest death rate is in the 20-24 years age group (Steentoft et al. 2006). Attempts should be made to motivate users to seek treatment (Darke & Hall 2003), also by EMS.

Needle-exchange programs and outreach services should be used for education of drug users not enrolled in treatment. Information on safer drug use (i.e. not to use drugs alone, avoidance of polydrug use etc.) should be distributed (Darke & Hall 2003). EMS personnel could be used either directly or as consultants on topics such as how to recognize an overdose, make a proper emergency call and administer bystander CPR. This could also help the development of confidence and trust in the EMS, help install mutual respect and thus hopefully lower the threshold of calling for help. The role of police in an overdose situation should also be considered. On the other hand, the safety of ambulance personnel should not be compromised.

Dispatcher assisted CPR instructions provided in overdose cases caused by opioids or other central nervous system depressants should include mouth-to-mouth ventilation in addition to chest compressions, similarly to CPR instructions in near-drowning and suffocation cases.

After treating an overdose, ambulance personnel could distribute leaflets and information on the possibilities of drug treatment (Pollini et al. 2006), recognition of overdoses and giving CPR. A team of outreach workers could be called to visit the location on the patient’s discretion. Non-healthcare
personnel like this, that are prone to meet overdose victims in their work, should be trained in overdose recognition and administering CPR. Staff of locations frequented by drug users, such as late night bars, cafeterias, fast food joints and service stations should also be informed on overdose recognition.

In the face of another heroin epidemic, naloxone should be distributed and training to use it provided to all ambulance personnel, not only paramedics. Necessary changes to appropriate guidelines should be made to allow this. Naloxone and the training to use it should be made available to non-healthcare personnel and drug users themselves. The legislation and logistics necessary for this should be addressed, as should be the follow-up for quality control and study purposes. More novel methods of naloxone administration, such as intranasal sprays, could be utilized. However, if heroin overdose patients are allowed to sign out after prehospital care, at least 0.4 mg of naloxone should be administered s.c. or i.m. to them (Table 17).

**Table 17: Proposals of topics for future studies**

<table>
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<th>Proposals</th>
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<tr>
<td>- Attitudes of dispatchers and ambulance personnel towards drug abusers</td>
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<td>- Attitudes of drug abusers towards emergency dispatching centre and ambulance personnel</td>
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<td>- Take home intranasal naloxone</td>
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<td>- Comparison of the duration of effect of s.c. versus i.m. naloxone</td>
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<td>- Serious overdoses caused by nonmedical use opioid analgesics</td>
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<td>- Prehospital recognition and management of designer drug overdose patients</td>
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