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# Acute poisonings:
# epidemiology and gastrointestinal decontamination

**by**

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ACADEMIC DISSERTATION

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**ABBREVIATIONS**

| | |
|---|---|
| AACT | American Academy of Clinical Toxicology |
| ac | activated charcoal |
| AUC(0-t) | area under the plasma drug concentration-time curve from zero to t hours |
| $C_{\Delta}$ | $C_{max}$ minus $C_{tp}$ |
| $C_{max}$ | peak plasma drug concentration |
| $C_{tp}$ | plasma drug concentration at the moment treatment was started |
| CI | confidence interval |
| CV | coefficient of variation |
| EAPCCT | European Association of Poisons Centres and Clinical Toxicologists |
| HPLC | high-performance liquid chromatograph |
| NA | not applicable |
| NSAID | non-steroidal anti-inflammatory drug |
| PEG | polyethylene glycol |
| SD | standard deviation |
| $t_{max}$ | time of peak concentration |
| wbi | whole-bowel irrigation |

## LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following publications. They will be referred to in the text by the Roman numerals I to VI.

**I** Lapatto-Reiniluoto O, Kivistö KT, Pohjola-Sintonen S, Luomanmäki K, Neuvonen PJ.
A prospective study of acute poisonings in Finnish hospital patients.
*Hum Exp Toxicol* 1998;17:307-311.

**II** Pohjola-Sintonen S, Kivistö KT, Vuori E, Lapatto-Reiniluoto O, Tiula E, Neuvonen PJ.
Identification of drugs ingested in acute poisoning: correlation of patient history with drug analyses.
*Ther Drug Monit* 2000; 22:749-752.

**III** Lapatto-Reiniluoto O, Kivistö KT, Neuvonen PJ.
Effect of activated charcoal alone or given after gastric lavage in reducing the absorption of diazepam, ibuprofen and citalopram.
*Br J Clin Pharmacol* 1999;48:148-153.

**IV** Lapatto-Reiniluoto O, Kivistö KT, Neuvonen PJ.
Gastric decontamination performed 5 min after the ingestion of temazepam, verapamil and moclobemide: charcoal is superior to lavage.
*Br J Clin Pharmacol* 2000;49:274-278.

**V** Lapatto-Reiniluoto O, Kivistö KT, Neuvonen PJ.
Efficacy of activated charcoal versus gastric lavage half an hour after ingestion of moclobemide, temazepam, and verapamil.
*Eur J Clin Pharmacol* 2000;56:285-288.

**VI** Lapatto-Reiniluoto O, Kivistö KT, Neuvonen PJ.
Activated charcoal alone and followed by whole-bowel irrigation in preventing the absorption of sustained-release drugs.
*Clin Pharmacol Ther* 2001; 70:255-260.

**ABSTRACT**

Hospital admissions due to poisonings are frequent, but studies concerning the pattern or the treatment of poisonings are few. Moreover, studies performed in different countries may not give the same results because of national characteristics. There is, however, a constant need for up-to-date information about acute poisonings so that prevention as well as treatment can be planned optimally. This thesis research began with studies concerning the epidemiology of poisonings in Finland. It continued with studies on the efficacy of the three gastrointestinal decontamination methods used worldwide in acute drug poisonings: activated charcoal, gastric lavage, and whole-bowel irrigation. These are all commonly used, but comparative studies concerning the effect of each treatment are limited.

A total of 271 patients and 36 healthy subjects took part in these studies. In the first prospective study the patients arriving at Helsinki University hospital with acute intoxication were examined and interviewed. The second study with patients also included the analysis of serum, urine, and gastric lavage samples, which were compared with the medical history taken on arrival. Gastrointestinal decontamination methods were studied in three-phase, randomised, and controlled studies with healthy volunteers. Volunteer studies were chosen in order to standardise many variables like drug doses, concomitant medications, and delay in presentation. The treatments compared activated charcoal alone vs. gastric lavage, activated charcoal alone vs. charcoal + gastric lavage, and activated charcoal alone vs. charcoal + whole-bowel irrigation. The treatments were started either immediately (5 min), 30 min, or 60 min after ingestion of the study drugs. The effect of the treatment was characterised by absorption of the study drugs, based on the area under the plasma concentration-time curve (AUC) and the peak plasma concentration ($C_{max}$).

The epidemiological studies showed that alcohol was involved in most cases in both genders either alone or together with drugs, but in younger people illegal drugs were more common than alcohol+drugs. The drugs involved in overdose cases were many, and no single drug could be identified as the leading agent. About half the patients had

taken more than one agent. The exact amount of drug taken was, however rarely remembered, and medical history was often unreliable, at least in part. In only 27% of the cases, the medical history was completely in accordance with laboratory findings.

The decontamination effect of activated charcoal alone and gastric lavage alone was compared in two studies. When the treatments were started immediately (5 min) after the ingestion of moclobemide, temazepam, and verapamil, activated charcoal reduced the absorption of the study drugs by 92 to 100% ($P<0.01$) compared with control values. The reductions in the charcoal phase were significantly larger than in the gastric lavage phase. When the time to treatment was postponed to 30 min, activated charcoal alone reduced the absorption of moclobemide and temazepam by 45 to 55% ($P<0.05$) and that of verapamil by 33% (P=n.s.). Gastric lavage reduced significantly only the absorption of moclobemide (44% $P<0.05$). Furthermore, the reduction of absorption of temazepam was significantly greater with charcoal than by lavage. The effect of activated charcoal alone and charcoal preceded by lavage was compared after a lag time of 30 min. Both charcoal alone and charcoal preceded by lavage reduced the AUC of diazepam, ibuprofen, and citalopram by 27% to 51% ($P<0.05$). There were no significant differences between treatments.

The sustained-release formulations of carbamazepine, theophylline, and verapamil were used to study the effect of activated charcoal alone and charcoal followed by whole-bowel irrigation. One hour after drug intake, charcoal reduced significantly ($P<0.001$) the absorption of all three drugs (by 62% to 75%). Whole-bowel irrigation did not increase significantly the effect of charcoal on any absorption parameter of the three drugs studied. On the contrary, the effect of charcoal followed by whole-bowel irrigation was significantly ($P<0.01$) worse than the effect of charcoal alone, but only for carbamazepine.

In conclusion, overdose cases presenting in hospitals often involve more than one agent. These agents are usually not reliably known during admission when treatment must be started. Furthermore, only 9% of patients presented within 1 h and 24% within 2 h of the ingestion of the poisonous agents. In two-thirds of the cases, the delay in presentation

was longer than 4 h. Accordingly, optimal treatment should prevent the effects of as many drugs as possible and during as wide a time-interval as possible. Activated charcoal alone seemed to be effective in reducing the absorption of the drugs when given either immediately, 30, or 60 min after drug ingestion, whereas gastric lavage alone seemed quite ineffective. When gastric lavage or whole-bowel irrigation is combined with activated charcoal the treatment may augment the effect of charcoal in preventing the absorption of some drugs - but may also decrease it. Therefore, in such overdose cases in which the drugs involved are known to be well adsorbable by charcoal, charcoal should be used without delay and other treatments only when they are known to bring additional benefit.

## INTRODUCTION

Poisonings are in many countries one of the most frequent reasons for admission to emergency departments, but trials concerning the management of intoxication are few. Furthermore, conclusions from epidemiological studies must be drawn with caution, since epidemiological characteristics differ among countries, which affects the results. In the UK, paracetamol is the most common drug used for self-poisoning (Hawton et al 1996), while in Finland paracetamol plays no major role in poisonings (Lamminpää et al 1993). Pesticides and other organophosphates are often involved in poisonings in developing countries but not so much in developed countries (Cabo Valle et al 1993, McLoone and Crombie 1996, Abdollahi et al 1997, Brito et al 1998). In Finland, one of the main features in poisonings has been a widespread use of alcohol and during recent years the growing use of mood-altering drugs.

Due to their special characteristics, intoxicated patients demand more care and time than do some other patient groups (Chan et al 1994, Lamminpää et al 1993, Thomas et al 1996b). Despite these time- and money-demanding features, treatment of poisoning is still mostly based on familiar routine or on specific case reports. Buckley and Smith (1996), seeking evidence-based data on management of antihistamine intoxication, identified 155 publications, of which 135 were single case reports concentrating on symptoms. Of the other 20 case series, only 7 described more than 7 patients. An obvious need thus exists for clinical trials of poisoning. General treatment of intoxication focuses on the maintenance of blood pressure, pulse, and breathing, but in severe cases the symptomatic follow-up is insufficient and the ingested drug should be eliminated. Three gastrointestinal decontamination methods are generally used in the treatment of acute overdose cases in Finland: activated charcoal, gastric lavage, and whole-bowel irrigation.

Gastric lavage was first introduced over 200 years ago (Major 1934) and is still used with activated charcoal, though some controversy exists as to its efficacy (Kulig et al 1985, Bosse et al 1995, Pond et al 1995). The efficacy of whole-bowel irrigation is not well documented, and the volume of irrigation solution or the time needed to perform

the irrigation are not based on knowledge, but on the few volunteer trials (Tenenbein et al 1987b, Rosenberg et al 1988, Kirschenbaum et al 1989). Activated charcoal was introduced as early as the nineteenth century (Cooney 1995) but was neglected until the second half of the twentieth. Since then, its efficacy in preventing the absorption of drugs has been studied intensively, and the benefit of activated charcoal in acute drug overdoses is widely agreed upon with some few limitations (Neuvonen and Olkkola 1988, Pond et al 1995). In 1993, the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) began to prepare a statement on gastric decontamination procedures. They concluded that in the management of poisoned patients none of the treatments should be administered routinely, and neither should any of these treatments be neglected (AACT; EAPCCT 1997 a, b, c).

The purpose of the first part of the studies was to perform epidemiological research on Finnish poisonings in order to learn the special characteristics in Finland in the late twentieth century and whether any evolution has occurred in physician's prescribing patterns. Also covered were the methods of treating poisonings and the correlation of anamnestic data with laboratory findings.

The other part of the present work comprised studies concentrating on the three general and most used gastrointestinal decontamination methods: activated charcoal, gastric lavage, and whole-bowel irrigation. These have all been used for decades in the prevention of absorption of drugs, although unanswered questions exist concerning their use. It has been generally accepted that the efficacy of gastric lavage decreases when the time-interval between ingestion and decontamination increases. For example, Auerbach et al showed a 90% recovery of liquid thiamine when lavage was performed 5 minutes after thiamine ingestion (Auerbach et al 1986). However, studies on the efficacy of lavage immediately after drug ingestion are few. Furthermore, no studies compare the efficacy of activated charcoal and gastric lavage immediately after drug ingestion. Neither does any study compare the efficacy of lavage followed by charcoal and activated charcoal alone. Whole-bowel irrigation is another gastrointestinal decontamination method often used together with activated charcoal. However, only one

study on healthy volunteers has compared activated charcoal alone and charcoal followed by whole-bowel irrigation, and this study has many limitations.

The present studies were designed to investigate the efficacy of activated charcoal alone, gastric lavage alone, activated charcoal preceded by gastric lavage, and activated charcoal followed by whole-bowel irrigation, all with time-intervals from 5 minutes to 1 hour. These studies were performed on healthy volunteers in order to standardise variables such as drug dose, concomitant medications, delay in presentation, and stomach contents.

# REVIEW OF THE LITERATURE

## 1. EPIDEMIOLOGY OF POISONINGS

Poisonings are on the whole an important and large group of causes leading to hospitalisation. The proportion of visits varies depending on type of emergency ward. In Australia, poisonings accounted for 20% of all admissions to the intensive-care unit and 5% of all medical-ward admissions (McGrath 1989). In China, they accounted for 3% of adult emergency department visits (Liu et al 1997), while in Turkey and in the UK only 1% of admissions to the emergency centre were poisonings (Özköse and Ayoglu 1999, Thomas et al 1996a). Irrespective of these differences in admissions, the mortality rates among patients admitted to hospital are very similar (<1%).

Irrespective of the rate of admissions there are also some other differences between different countries as well as between adult and childhood poisonings. In developed countries, the leading causes of adult poisonings are drugs and alcohol (Jacobsen et al 1984, Cabo Valle et al 1993), while in developing countries pesticides are also commonly involved (Abdollahi et al 1997, Leveridge 1999). In Finland in deaths due to poisoning, drugs and alcohol are the leading components, and levomepromazine has been the commonest drug in deaths since 1996; in 1999 it was found in 60 patients. In children, the leading causes of hospital admissions due to poisoning are non-drug substances like plants, berries, and mushrooms (Lamminpää et al 1993). Due to these differences, epidemiological aspects of poisonings have their own features in every country, and only limited conclusions can be drawn from other countries.

Data from epidemiological studies are needed, however, to monitor the changing patterns of poisonings and to provide guidance for effective poison-prevention programs. A good example of this was seen in the UK, where paracetamol was found to be a leading agent of poisonings (Fagan and Wannan 1996, Hawton et al 1996, McLoone and Crombie 1996). Since the introduction of new UK regulations that limit the availability of paracetamol, a substantial decrease has taken place in the occurrence and severity of cases of paracetamol overdose (Turvill et al 2000). In Finland, these

regulations would have no significant effect because paracetamol does not play such a major role (Lamminpää et al 1993).

Most of the epidemiological studies have been retrospective, and in many prospective studies as well, information on the poisonous agent is gathered from the medical history. The reliability of this anamnestic information has varied from 45% to 86% (Wright 1980, Rygnestad et al 1990). This large difference between medical history and laboratory screening has been explained by patients' forgetting some agents taken and possibly vomiting before reaching hospital. Because of these inaccuracies in information gained at admission, treatment must be suitable for as many drugs as possible.

## 2. MANAGEMENT OF ACUTE DRUG POISONINGS

The treatment of acute drug poisoning is based on some general principles. After determining which drugs and how many tablets or capsules have been ingested, management should be targeted to prevent and treat the symptoms caused. Because many drugs affect the central nervous system, ventilation and circulation must therefore be carefully followed and supportive treatment started. Possible arrhythmias and seizures are treated with specific drugs. Some intoxication can be treated with an antidote, but there is no antidote against most drugs. Some drugs can be cleared from the blood via haemodialysis or haemoperfusion, but these procedure are not effective in every case.

However, in severe intoxication the symptomatic and supportive treatment is not enough; absorption of ingested drugs should be prevented and/or their elimination should be enhanced. The main gastrointestinal decontamination methods are activated charcoal, gastric lavage, ipecac-induced emesis, and whole-bowel irrigation.

Vomiting, either spontaneous or by induced emesis with has seemed a rational treatment if the poisonous agent has been ingested and is not corrosive. Emesis induced by ipecacuanha syrup is, however, rather ineffective, and more effective methods like

gastric lavage have displaced it. Another mechanism introduced to reduce the harmful effect of a poison is whole-bowel irrigation and some cathartics. These should carry the poisonous agent more quickly through the intestine and thus allow less time for absorption. The third mechanism is to prevent the absorption; activated charcoal has served that purpose.

Recommendations regarding the use of these treatments have been confusing for decades (Matthew et al 1966). It was, however, only in the 80's that comparison studies between different treatments began (Tenenbein et al 1987a, Danel et al 1988, McNamara et al 1989). However, in overdosed patients, the considerable heterogeneity of poisonings makes comparison of different treatments difficult. There are only a couple of large clinical studies evaluating the effect of gastric lavage, activated charcoal, or ipecacuanha-induced emesis (Kulig et al 1985, Merigian et al 1990, Pond et al 1995). Though these studies were well conducted, they were unable to produce clear guidelines as to which treatment should or should not be used. Whole-bowel irrigation is even less studied, and there is no clinical report on its efficacy.

Many patients who present to hospital because of intoxication are otherwise healthy and resemble the subjects used in volunteer studies. The benefit of volunteer studies is thus their ability to standardise variables such as drug dose, concomitant medications, and delay in presentation; with these standardised variables comparison of different treatments is more reliable.

A short conclusion from earlier studies is that ipecacuanha-induced emesis is not as effective as activated charcoal (Neuvonen et al 1983b, Neuvonen and Olkkola 1984a, Tenenbein et al 1987a, Albertson et al 1989) or gastric lavage (Auerbach et al 1986, Tandberg et al 1986), and in general, it should not have a place in the management of poisonings, at least of adults. However, the position of activated charcoal and gastric lavage has remained unclear and even controversial despite many clinical as well as volunteer studies (Jones and Volans 1999). Studies concerning the use of whole-bowel irrigation are few, but this method is still used quite widely without any questioning of its efficacy or safety.

# 3. GASTROINTESTINAL DECONTAMINATION METHODS

## 3.1. Activated charcoal

### 3.1.1. General aspects of charcoal

Activated charcoal was first introduced in France in the nineteenth century and is mentioned now and then in the medical literature of the first half of the twentieth century (Olkkola Thesis 1985). The first proper studies with activated charcoal were, however, performed first in the 1940's (Andersen 1946, 1947), after which the benefits of charcoal were recognised and its use as a treatment of poisonings began to increase. All the knowledge was based on in vitro studies until the first controlled volunteer studies were made in the 1970's. Now activated charcoal is one of the most studied gastrointestinal decontamination methods in poisonings, with over 100 volunteer or patient studies on its efficacy.

Charcoal is produced from the pyrolysis of coconut shells, peat, lignite (coal), wood, or petroleum and it is activated by heating in steam, air, or carbon dioxide at 600-900°C. Then charcoal is washed with inorganic acids and dried. Activation creates a highly developed internal pore structure and small particle size. The antidotal efficacy of activated charcoal depends on its dose, pore size, and internal surface area, on the stability of the charcoal-drug complex, and the charcoal:drug ratio, on the pH of the environment, and the gastrointestinal contents, as well as on the delay in administration (Olkkola Thesis 1985, Neuvonen 1982, Watson 1987, Neuvonen and Olkkola 1988).

Activated charcoal is usually given in a water suspension. Co-operative patients can drink it and others receive it through a naso- or orogastric tube. The usual amount for adults is 50 g once, but the dose can be repeated if necessary. Activated charcoal can be used alone for treatment of poisonings but can also be combined with gastric lavage (charcoal following lavage) or whole-bowel irrigation (charcoal preceding irrigation).

### 3.1.2. In vitro studies

Many in vitro studies produce results which can, however, not be applied directly in clinical situations (Andersen 1946, 1947, Neuvonen and Kannisto 1984, Olkkola 1984, Cooney 1995). The benefit from these studies is mainly to identify those agents not adsorbed by charcoal as well as to show several factors which affect this adsorption process. For example, most metals, like lithium and iron, are not efficiently adsorbed by charcoal (Neuvonen and Olkkola 1988). Furthermore, alcohol, which is often involved in acute poisonings together with drugs, is poorly adsorbed to charcoal (Neuvonen and Olkkola 1988). The effect of ethanol on the adsorption capacity of charcoal was studied by Neuvonen et al (1984), who found that in vitro, ethanol (10%) significantly reduced the adsorbed fraction of aspirin, quinidine, and amitriptyline, whereas in healthy human volunteers, the concomitant ingestion of ethanol (50g) had no significant effect on the ability of the charcoal to reduce the absorption of aspirin or quinidine. In this in vitro study, the adsorption of aspirin, quinidine, and amitriptyline was also dependent on pH, in line with Andersen (1947) who showed that acids are best adsorbed by charcoal in an acidic environment and bases in an alkaline environment (i.e., in non-ionised form). The clinical importance of this finding is, however, minor (Olkkola and Neuvonen 1984a) offering no reason for antacids together with charcoal to treat poisoning from acidic drugs. Gastric contents have been found to modify the efficacy of charcoal slightly (Olkkola and Neuvonen 1984b), but the most important factor seems to be the charcoal-drug ratio (Olkkola 1985). At a ratio of 10:1, 90 to 100% of most drugs is adsorbed by charcoal in in vitro conditions (Neuvonen and Olkkola 1988). In acute poisoning the effect of gastric contents, possibly alcohol, the lag time, and the unknown amount of a poisonous agent complicate the situation and reduce the efficacy of charcoal. Therefore, the dose of charcoal should be large enough (50-100g) to minimise the risk of saturation of its adsorption capacity; the ratio of 10:1 may not be sufficient in clinical situations.

### 3.1.3. Volunteer studies

In order to standardise many factors possibly affecting the adsorption capacity of charcoal, such as gastric contents and other drugs taken simultaneously, most studies are

performed with healthy volunteers. The effect of activated charcoal on different drugs has been extensively examined, since the results from one drug cannot be extrapolated directly to others. The difficulty of comparing these volunteer studies with each other involves the differing time-intervals between ingestion of a drug and of charcoal as well as the differing doses and qualities of the charcoal.

The dose of activated charcoal may be the most important factor limiting the prevention of absorption of drugs. The first volunteer studies as well as clinical recommendations involved small amounts of charcoal (1 - 10g) (Levy and Houston 1976, Dawling et al 1978), which made charcoal seem ineffective. In the study of Levy and Houston (1976), charcoal (5 or 10 g) reduced the absorption of paracetamol on average only by 54% when administered immediately after the ingestion of the drug, whereas a larger immediate dose of charcoal (50 g) reduced the absorption of paracetamol by 80% (Neuvonen et al 1983b). In the study of Yeates and Thomas (2000) a dose of 50 g was able to reduce the absorption of paracetamol by 56% even 1 h after the ingestion. The first controlled studies on the effect of higher doses (i.e. 50 g) of activated charcoal were published in the 1970's (Neuvonen et al 1978), and now there are over 20 volunteer trials in which clinically relevant doses of 25 g or 50 g of charcoal have been administered immediately after drug ingestion. Reduction in absorption in these trials has usually been over 90% (Kärkkäinen and Neuvonen 1986, Neuvonen and Elonen 1980, Neuvonen et al 1992, Laine et al 1997a), ranging from 57% for salicylate in the study by Neuvonen and Olkkola (1986) to 100% for diphenhydramine in the study by Guay et al (1984).

In those 20-some studies, charcoal was administered immediately after drug ingestion. Another important factor affecting the capacity of charcoal to adsorb drugs is the time-interval between drug ingestion and charcoal ingestion. In volunteer studies, this time-interval has varied from 0 to 360 minutes (AACT, EAPCCT 1997b, Laine Thesis 1997). When data from these over 100 different studies concerning 43 drugs are summarised, it seems evident that the effect of charcoal diminishes with increasing time-interval.

When activated charcoal is administered 30 min or more after drug ingestion the reduction in the absorption of drugs is already diminished. The variation of reduction in absorption is quite large: from 31% to 75%, and on average 54% (Levy and Houston 1976, Dawling et al 1978, Sintek et al 1979, Sketris et al 1982, Neuvonen et al 1983b, Ekins et al 1987). As summary of the studies with 50 g activated charcoal and a 1-h time-interval shows a reduction of 37%, though even here the variety was large, and in the study of Minton et al (1995) charcoal prevented the absorption of sustained-release theophylline by 83%. The studies with longer than a 1-h time-interval show a reduced efficacy in the charcoal's antidotal capacity. In the study of Laine et al (1997b) the reduction of absorption of pholcodine was at 2 h 26%. In another study by Laine et al (1996), however, charcoal no longer reduced significantly the absorption of fluoxetine at 2 h.

The formulation of the drug affects the antidotal efficacy of charcoal together with time-interval, and the reduction in absorption of sustained-release formulations may still be significant 4 h after ingestion of the drug (Laine et al 1997c).

Two volunteer studies have compared activated charcoal (50 g), emesis and gastric lavage (Tenenbein et al 1987a, Danel et al 1988). In Tenenbein et al (1987a), lavage reduced the absorption of ampicillin by 32%, emesis by 38%, and charcoal by 57%. On the other hand, when Danel et al (1988) studied aspirin, all three methods reduced the recovery of salicylate in urine by about 50%, which was almost the same reduction as in the control phase. The efficacy of charcoal was better in the study by Christophersen et al (1999), who compared charcoal alone with a combination of charcoal and lavage. Charcoal alone reduced the absorption of paracetamol by 60% 1 h after the ingestion of tablets, whereas the combination treatment reduced it by 54%. No other volunteer studies cover charcoal and lavage or emesis, and the comparisons with whole-bowel irrigation are also limited (Rosenberg et al 1988, Kirschenbaum et al 1989, Mayer et al 1992). In the study of Rosenberg et al, activated charcoal was superior to whole-bowel irrigation when the treatment was started immediately after the ingestion of aspirin tablets; charcoal reduced the absorption by 79%, whereas whole-bowel irrigation reduced it by only 24%. On the other hand, whole-bowel irrigation was more effective

in the study of Kirschenbaum et al (1989) in which lag time was 4 hours and the tablets were entero-coated salicylate tablets; here the mean reduction in absorption of salicylate was 57% for charcoal and 73% for whole-bowel irrigation. However, neither treatment was effective when Mayer et al (1992) studied their effect on enhancing the excretion of aspirin during the postabsorptive phase: Aspirin was given as a suspension, with treatments started 4 h later.

### 3.1.4. Clinical studies

As there are many difficulties in conducting a proper clinical study with poisoned patients, the number of such trials is very limited. Only one well-conducted clinical trial used activated charcoal in only one study arm. Underhill et al (1990) compared charcoal with gastric lavage, or ipecac-induced emesis, with 60 patients who had taken a paracetamol overdose randomised to receive either charcoal, lavage, emesis, or no treatment at all. The no-treatment group was halted for ethical reasons in the middle of the study. The others were followed and paracetamol plasma levels were measured. The mean fall in paracetamol plasma level was 52%, 39%, and 41% for charcoal, lavage and emesis, respectively. Only charcoal results differed significantly from those of the other treatments.

The largest clinical trials all had the same protocol, comparing activated charcoal alone with charcoal combined with either gastric lavage or ipecac-induced emesis. The first of these studies was performed by Kulig et al (1985), who studied 592 acute drug-overdose patients. Patients arriving on even-numbered days received no gastric emptying procedures but only 30 to 50 g charcoal; these were compared with patients arriving on odd-numbered days who received either gastric lavage or ipecac-induced emesis as well as charcoal. Emesis was performed on alert and co-operative patients, and lavage was performed on obtunded, convulsing, intubated, or uncooperative patients. The efficacy of the treatments was assessed by dividing the patients into three classes: mildly, moderately, and severely intoxicated, and by determining whether the patients clinically improved or deteriorated after the initial treatment. In this study, emesis did not alter the clinical outcome of alert patients, but charcoal alone was as effective as the combination

treatment. The only significant difference was between gastric lavage+charcoal and charcoal alone in obtunded patients; combination treatment was more effective than charcoal alone when lavage was performed within 1 h of ingestion. It must be noticed, however, that the numbers of these obtunded patients arriving within 1 h were only 16 and 3 in both groups. Furthermore, the two other studies with the same protocol were unable to confirm these results. In the study of Merigian et al (1990) with 808 patients, gastric emptying was not more effective in any patient group, and lavage was actually associated with a higher prevalence of medical intensive care unit admissions (P=0.0001) and aspiration pneumonia (P=0.0001). Pond et al (1995) performed their study by the same method, and with 876 patients, there were no significant differences in efficacy or safety between those patients who underwent gastric emptying and those who did not.

The efficacy of charcoal alone was also confirmed in two other studies. Bosse et al (1995) compared activated charcoal alone to charcoal combined with lavage in tricyclic antidepressant overdoses and found no statistically significant differences among 51 patients. Albertson et al (1989), on the other hand, compared charcoal alone with ipeca-induced emesis+charcoal. Though Tenenbein et al (1987a) had reported a significant reduction in absorption of ampicillin both by charcoal and by emesis in their volunteer study, charcoal alone was more safe and effective. Patients were discharged significantly sooner and experienced fewer complications without emesis.

### 3.1.5. The position of activated charcoal

The international Position Statement (AACT, EAPCCT 1997b) states that benefit from the use of charcoal has not been satisfactorily demonstrated, and charcoal may be considered only if a patient has ingested a toxic amount of poison up to 1 h previously. This statement does not, however, take note of modified-release drugs at all. The trials of these drugs are not many, but in one trial, Laine et al (1997c) showed that charcoal given even 2 or 4 h after ingestion of slow-release verapamil reduced the absorption of the drug significantly.

To sum up all the volunteer studies, the efficacy of activated charcoal diminishes with increasing time-interval. Since this decrease is not linear, there is no exact time-point after which administering charcoal would have no more effect, but charcoal should be given as soon as possible. The clinical trials, on the other hand, showed that activated charcoal had no significant complications when used alone, and it was always at least as effective as lavage or emesis. In the light of all the studies mentioned, it seems sensible that the use of gastric emptying has decreased and the use of charcoal increased (MacNamara et al 1996). The international Position Statement (AACT, EAPCCT 1997b) did not, however, rate any of the gastrointestinal decontamination methods as better than the others. The use of activated charcoal is, however, limited to those drugs adsorbed by charcoal and it should also be avoided when the patient has ingested a corrosive material.

## 3.2. Gastric lavage

### 3.2.1. General aspects of lavage

Gastric lavage is a medical action to empty the stomach of its contents. It originated in the eighteenth century when Munro Secundus designed a stomach pump for the treatment of domestic animals (Burke 1972). Several decades passed before this system was used in treatment of human poisoning. The first known lavage was performed in Pennsylvania in the USA, where Dr. Physick used a syringe and tube on twin children with whooping cough who had received large quantities of laudanum. He washed them out with brandy and water. One child died and the other survived (Burke 1972). Controversy as to the efficacy of gastric lavage had begun.

Gastric lavage is now performed with an orogastric tube and a syringe. During lavage, warm tapwater is used in 200 ml aliquots, and gastric content is aspirated through the lavage tube immediately after every or every other aliquot. This is continued as long as the returns are clear, with usually about 2 l of water used. The optimal position for a patient would be lying on his left side with the head lower than the hips. This position can be achieved in volunteer studies but usually not with patients who resist the

procedure and are allowed to maintain a sitting position. Because of lack of co-operation at least two nurses are needed to perform a lavage which lasts from 15 to 20 minutes.

The characteristics of gastric lavage have evoked conflicting statements on its use (Kulig et al 1985, Merigian et al 1990). Obviously it can remove at least a portion of a poisoning agent from the stomach but probably not all. It has also been thought to propel the stomach contents into the intestine and reduce the efficacy of activated charcoal. Moreover, the time required to perform lavage delays the use of activated charcoal. As lavage is rather unpleasant to the patient as well as time- and staff-consuming, the desirability of performing gastric lavage has been questioned (Danel et al 1988).

### 3.2.2. Volunteer studies

When gastric lavage was first introduced, it was used alone for treatment of poisonings. After the advance of activated charcoal, these two treatments have usually been combined. However, volunteer studies have concentrated on comparison of lavage alone with other treatments. Tandberg et al (1986) compared gastric lavage and ipeca-induced emesis (30 ml), using cyanocobalamin (vitamin B12) as a marker in 18 volunteers. Lavage was performed with subjects placed in the left lateral decubitus position with the head of the bed lowered 10 degrees. Ten minutes after the ingestion of 25 tablets each of 100 μg vitamin B12, lavage or ingesting ipecac began. Lavage was significantly more effective ($P<0.005$) than emesis, and the recovery of the marker was 45% vs. 28%. The exact opposite result was achieved in the study of Young and Bivins (1993), though the amount of ipecac and the performance of lavage were the same. In their study, 19 volunteers ingested 30 capsules labelled with a measured amount of $Tc^{99m}$. Immediately after the ingestion either emesis or lavage was started; ipecac-induced emesis was significantly more effective than gastric lavage. Emesis returned 54% of the marker and lavage only 30% ($P=0.0021$). Three other volunteer studies compared ipecac-induced emesis, gastric lavage, and activated charcoal, with a lag-time in each of 1 h (Tenenbein et al 1987a, Danel et al 1988, Minton et al 1995). These studies showed no significant differences between ipecac-induced emesis and gastric lavage, and activated charcoal

was the only treatment with results which differed from those of the control group in each study.

In only one volunteer trial was gastric lavage combined with activated charcoal, and this combination treatment was compared to that with activated charcoal (Christophersen et al 1999). Gastric lavage seemed not to add any benefit to charcoal use. The reductions in absorption of paracetamol 1 h after its ingestion were 60% for activated charcoal alone and 54% for gastric lavage followed by activated charcoal.

### 3.2.3. Clinical studies

Results from the volunteer studies have been contradictory and have inspired some new questions. Gastric lavage has been thought to force gastric contents into the small intestine, thus increasing the amount of drug available for absorption and decreasing the amount available to specific antidotes or charcoal. Saetta et al (1991) studied 60 patients coming to an emergency department because of poisoning. Each was asked to swallow 20 radio-opaque pellets, after which the 60 were divided into three equal groups. Those thought medically to require gastric emptying received either gastric lavage or ipecac-induced emesis, and those who did not require it served as controls. After the treatments, the number of residual pellets was assessed by x-ray. The time-lapse for the control group between ingestion of the pellets and the x-ray varied between 30 and 70 minutes. The same time was needed for gastric emptying procedures. After both treatments, over 30% of the pellets were counted in the small intestine, significantly more than in the control group. Neither treatment was able to remove all the contents from the stomach; after lavage 52% and after emesis 59% of the pellets were retained in the gastrointestinal tract. The same kind of result was obtained in another study, by Saetta and Quinton (1991), who compared lavage and emesis in 30 self-poisoned patients. After these procedures, all patients were endoscoped, and a visual assessment was made concerning the amount of solid and liquid residue in the stomach. There was no statistical difference between the treatments, and both food and tablets were visible in gastroscopy.

Clinical studies can also be divided into those which compare gastric lavage alone to other treatments and those with combined gastric lavage and activated charcoal. Gastric lavage and ipecac-induced emesis was compared by Auerbach et al (1986). In their study 88 patients received either emesis or lavage based on level of consciousness or refusal to drink syrup of ipecac. Before the procedures, each received 100 mg of liquid thiamine as a marker. In the lavage group, the recovery of thiamine was 90% and in the emesis group 50%, a significant difference. That kind of difference was not achieved by Underhill et al (1990) who compared lavage, emesis, and activated charcoal in the management of paracetamol overdose. For 60 patients, the mean percentage fall in plasma paracetamol levels was 39% for lavage, 41% for emesis, and 52% for charcoal. Emesis seemed a little more efficient than lavage, but the difference was not statistically significant, whereas charcoal differed significantly from the other treatments.

These studies all have measured either the recovery of a marker or a reduction in absorption of the poisoning-causing drug. There are, however, four prospective clinical studies which compared different treatments and had clinical endpoints. Kulig et al (1985) recruited 592 overdose patients to compare ipecac-induced emesis + charcoal, gastric lavage + charcoal, and activated charcoal alone. In this study, emesis gave no clinical benefit to patients who were alert and awake on admission. For only 16 patients, who presented within 1 h and were obtunded, was lavage found to be beneficial. The same protocol was tested by Merigian et al (1990) and Pond et al (1995). Merigian et al recruited 808 patients who received either activated charcoal alone or charcoal combined with gastric emptying. No clinical deterioration occurred in the patients treated without gastric emptying; gastric lavage was actually associated with a higher proportion of medical intensive care unit admission ($P=0.0001$) and aspiration pneumonia ($P=0.0001$) than was lavage+charcoal. In the study of Pond et al, 876 patients received either charcoal alone or charcoal combined with gastric emptying. In contrast with the two previous studies, no statistically significant differences existed between study groups, but both clinical course and complications were the same with all treatments.

Nor were any clinical differences were found by Bosse et al (1995), who compared activated charcoal alone, lavage+charcoal, and charcoal+lavage+charcoal. In that study, 51 patients with a tricyclic antidepressant overdose received one of these treatments, and no statistically significant differences were found between the groups.

### 3.2.4. The position of gastric lavage

Neither voluntary trials nor patient studies have been able to confirm or deny the benefit of gastric lavage. The amount of drug removed from the stomach has varied widely (Auerbach et al 1986, Young and Bivins 1993, Minton et al 1995), and the effect on the clinical course of the patient has not been unambiguous (Kulig et al 1985, Merigian et al 1990). The recent Position Statement (AACT, EAPCCT 1997a) has been unable to give simple recommendations for its use but says "Gastric lavage should not be considered unless a patient has ingested a potentially life-threatening amount of a poison and the procedure can be undertaken within 60 minutes of ingestion". The difficulties for the clinician are estimation of the amount taken as well as estimation of ingestion-time (DaCruz 2000). In addition the value of gastric lavage depends on the place/country where poisoning occurs. In developing countries where highly toxic organophosporus compounds (usually consumed in liquid form) and aluminium phosphide are common, prevention of even small amounts of absorption makes a difference. Furthermore, although antidotes and intensive care units may not be available, gastric lavage can be carried out rather easily (Bhattarai 2000). However, gastric lavage should not be performed when the patient has ingested a corrosive substance such as a strong acid or alkali, or a hydrocarbon with high aspiration potential. Neither should it be done to the patient in a depressed state of consciousness.

## 3.3. Whole-bowel irrigation

### 3.3.1. General aspects of whole-bowel irrigation

Whole-bowel irrigation cleanses the bowel with an osmotically balanced polyethylene glycol electrolyte (PEG) solution. This solution is usually given by nasogastric tube but

the patient can also drink it. The procedure is meant to reduce drug absorption in the bowel, to expell the poisonous agent from the body and to induce liquid stools. It does not change the water or electrolyte balance of the patient. Whole-bowel irrigation has been used clinically in radiology, gastroenterology, and surgery when the bowel of the patient must be emptied, as before colonoscopy or colongraphy. For the management of poisonings it has been used for some decades, but no clinical trials of its efficacy exist.

### 3.3.2. In vitro studies

Whole-bowel irrigation is normally used together with activated charcoal, and the possible interactions of these two methods have been studied in vitro. Only one study examined both the changes in osmotic properties of the irrigating solution and whether the absorptive capacity of the charcoal is changed (Kirschenbaum et al 1990). In the first part of the study, serial ratios of PEG solution and activated charcoal powders were added to water, and the solutions were analysed for PEG concentration and osmolality. In the second part, serial ratios of PEG solution and charcoal preparation were combined with a constant amount of salicylic acid. Solution osmolalities, PEG, and salicylic acid concentrations were then quantified. The results showed no clinically important changes in osmolality of solutions, nor was adsorption of salicylic acid by charcoal significantly changed, although it decreased with increasing concentration of PEG solution. The conclusion of another four in vitro studies is that activated charcoal should not be mixed with the PEG solution but rather be given first (Hoffman et al 1991, Arimori et al 1992, Arimori et al 1993, Makosiej et al 1993).

### 3.3.3. Volunteer studies

Though whole-bowel irrigation is, in general, clinically combined with activated charcoal, in only one study did the protocol do this (Rosenberg et al 1988). Among the methodological problems in this study were the few (only three) volunteers. The other studies compared whole-bowel irrigation either with charcoal alone or with a control. A study group from Canada performed three studies in which they used ampicillin (Tenenbein et al 1987b), delayed-release aspirin (Kirschenbaum et al 1989), and

ordinary aspirin (Mayer et al 1992) as markers. The protocols were very similar to each other. Nine or ten volunteers received the irrigation solution through a nasogastric tube at an average rate of 2 l/h. The intervention was terminated when the rectal effluent became visibly similar to the infusate, at minimum time of 3 h and maximum of 5 h. The mean volume infused was 7.4 to 7.7 l. Whole-bowel irrigation prevented more effectively than the control treatment (=no treatment) the absorption of ampicillin, and more effectively than did activated charcoal (50 g charcoal in 70% sorbitol suspension) the absorption of delayed-release aspirin. When the intervention was started 4 h after the ingestion of ordinary aspirin, neither charcoal nor whole-bowel irrigation values differed from control values. Smith et al (1991) studied the efficacy of whole-bowel irrigation on the prevention of absorption of sustained-release lithium and found the irrigation to prevent the absorption significantly better than did the control. The protocol of this study resembled those of earlier volunteer studies: the solution was given through a nasogastric tube, and the amount was 10 l administered over 5 h.

The different volumes of PEG solution have been studied only by Olsen et al (1995) who compared use of 3 l and 8 l of the PEG solution. Both were given at the rate of 2 l/h in a randomised cross-over study with nine volunteers. They found the smaller amount to prevent the absorption of ibuprofen as well as did the 8 l. More trials are, however, needed to find the optimal volume as well as rate of administration of PEG solution.

### 3.3.4. The position of whole-bowel irrigation

These studies and some case reports (Turk et al 1993, Buckley et al 1993) have been unable to give precise recommendations as to when and how whole-bowel irrigation should be performed. Such irrigation may be considered for potentially toxic ingestion of sustained-release or enteric-coated drugs and remains a theoretical option for iron, lead, zinc, or other agents non-adsorbable by charcoal. When used together, PEG solution and charcoal should not be mixed, but a single dose of charcoal should be given first. Whole-bowel irrigation is contraindicated when the patient has bowel obstruction, perforation, or ileus, or for patients with haemodynamic instability or compromised unprotected airways (AACT; EAPCCT 1997c).

# 4. SOME ASPECTS OF THE STUDY DRUGS

## 4.1. Carbamazepine

Carbamazepine is an iminodibenzyl derivative the structure of which is related to the tricyclic antidepressants (Dollery 1991). Its oral bioavailability has been 58 to 80% in animal studies, but there exists no suitable parenteral preparation of carbamazepine for pharmacokinetic studies in man (Morselli et al 1973). The gastrointestinal absorption of carbamazepine has been estimated at 72 to 96% (Faigle and Feldmann 1975, Levy et al 1975) with peak plasma concentrations occurring between 6 and 24 h (Pynnönen 1979). The half-life following a single dose is 30 to 40 h, whereas on multiple dosing it decreases to 12 h because of autoinduction of carbamazepine metabolism (Dollery 1991). Carbamazepine is 75% bound to plasma proteins and is eliminated in the urine mainly as metabolites. Carbamazepine is generally used as sustained-release tablets in order to avoid central side-effects.

Carbamazepine is used for the treatment of complex and simple partial seizures, tonic-clonic generalised (grand mal) seizures, and trigeminal neuralgia, and for psychiatric conditions like sleep disturbances during alcohol-withdrawal syndrome. The normal dose is 400-mg two or three times daily, but some patients need up to 2400 mg daily. Acute carbamazepine poisoning is dominated by neurologic features, but cardiovascular effects are also common (Faisy et al 2000). More severe cases are characterised by central nervous system depression. Survival in adults has been reported after ingestion of as much as 640 mg/kg (Patsalos et al 1987). Toxicity has been demonstrated when serum concentrations have exceeded 20 mg/l (Leslie et al 1983), and concentrations of 40 mg/l or higher have been associated with an increased risk of serious complications like coma, seizures, and cardiac conduction defects (Höjer et al 1993). The peak plasma concentration after one 400 mg tablet is usually 4.5 mg/l. Death after carbamazepine overdose is uncommon but may result from cardiac arrhythmia, aspiration pneumonitis, hepatitis, or status epilepticus (Sharma et al 1991).

Treatment of carbamazepine poisoning consists of supportive measures. Gastric lavage may be indicated if a patient has taken a massive overdose. A time-interval of 1 h has been recommended (Jones and Proudfoot 1998), but as the drug itself reduces gastrointestinal motility, no restrictions have been given. Carbamazepine is adsorbed by charcoal (Neuvonen et al 1988). When charcoal is administered 5 min after drug ingestion it prevents absorption of carbamazepine almost completely, and 1 h after drug ingestion it has prevented the absorption by 59% (Neuvonen and Elonen 1980). As carbamazepine has a long half-life and a considerable enterohepatic cycle, charcoal given in multiple doses during the postabsorption phase can prevent the enteral reabsorption of carbamazepine. Neuvonen and Elonen (1980) have shown the effect of multiple dose charcoal on the elimination of carbamazepine to be almost as good as that of haemodialysis. In their study the total plasma clearance of carbamazepine rose from 22 ml/min to 40 ml/min, whereas haemodialysis increased it to about 48 ml/min (Lee et al 1980). Haemoperfusion is, however, used for severe intoxications.

### 4.2. Citalopram

Citalopram is rapidly absorbed from the gastrointestinal tract, with the $C_{max}$ attained 2 to 4 h after an oral dose (Kragh 1981). Absorption is practically complete (100%). Citalopram and its metabolites are 70 to 80% bound to plasma proteins (Cipramil: Technical monograph 1989). It is slowly eliminated ($t_{1/2}$ = 33 h), primarily by hepatic metabolism that exhibits polymorphism; only 13% of the dose is excreted unchanged in the urine.

Citalopram is an antidepressant agent which enhances serotoninergic neurotransmission through selective and potent inhibition of serotonin reuptake (Dollery 1991). The main indication is depression, but it can aid also in panic disorder and substance abuse. The usual oral dose is started at 20 mg daily, and the dose is titrated based on efficacy and side-effects up to 60 mg. For elderly patients, the recommended dose is 10 to 30 mg, due to the longer half-life in the elderly. In Sweden, when 44 cases of acute citalopram overdose were studied (Personne et al 1997), doses below 600 mg caused only mild symptoms, and doses higher than 600 mg caused ECG abnormalities and convulsions in

some patients. Doses above 1900 mg caused such symptoms in all patients. Though citalopram is less toxic than tricyclic antidepressants, it can cause a fatal serotonin syndrome when taken together with monoamine oxidase (MAO) inhibitors (Neuvonen et al 1993), and this combination should be avoided.

The recommended treatment of citalopram overdose is symptomatic and supportive. The effect of activated charcoal has not been studied, and gastric lavage is recommended in the older literature if the patient presents within 4 h of ingestion (Dollery 1991).

### 4.3. Diazepam

Diazepam is the most widely used benzodiazepine. It is absorbed rapidly and completely after oral administration, with its $t_{max}$ at 15 to 90 min in adults and 15 to 30 min in children. A secondary peak appears 6 to 12 h after ingestion, possibly due to enterohepatic recirculation. Diazepam is highly (98-99%) bound to albumin. It is mainly metabolised in the liver and has three active metabolites: N-desmethyldiazepam, oxazepam, and temazepam. The plasma half life for diazepam is 20 to 100 h and for N-desmethyldiazepam 30 to 200 h (Dollery 1991).

The main indication for diazepam is the treatment of anxiety. It is also used for acute alcohol withdrawal and for treatment of status epilepticus and other convulsive states (parenteral formulations). Because of its wide clinical use, diazepam is also the most common benzodiazepine in poisonings (Buckley et al 1995). The usual therapeutic doses are 2 to 10 mg orally 1 to 4 times daily. After repeated doses of 5 mg three times daily, the steady-state plasma concentration has reached 250 to 300 ng/ml. The lethal dose of diazepam in man is unknown and no deaths have been reported following diazepam overdose alone. In the overdose study of Divoll et al (1981a), plasma diazepam levels ranged from 585 to 8635 ng/ml and doses had been as high as 750 mg. However, several deaths have resulted from the co-ingestion of other central depressants like alcohol (Divoll et al 1981a, Höjer et al 1989). The main symptoms of acute overdose are the enhancement of the therapeutic effects leading to drowsiness, oversedation, reduced reflexes, and then coma. The effect on respiration, pulse or blood

pressure is usually not significant unless diazepam has been combined with other centrally acting drugs.

Treatment of overdose is usually symptomatic, but in severe cases there is a specific antidote, flumazenile, against diazepam as well as other benzodiazepines. The effect of activated charcoal on the absorption of oral formulations of diazepam has not been studied.

### 4.4. Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) derived from propionic acid. It is rapidly ($t_{max}$ 1-2 h) and almost completely absorbed after oral dosing, the bioavailability being around 90%. It is highly (99%) bound to plasma albumin and rapidly eliminated from the plasma, with a half-life of about 2 h (Adams et al 1969). It is metabolised in the liver, and more than 90% of the dose is excreted in the urine (Dollery 1991).

Ibuprofen has a prominent anti-inflammatory effect as well as analgesic and antipyretic effects. Its therapeutic indications are thus the same as for other NSAIDs, such as musculoskeletal pain, arthritis, gout, postoperative pain, and migraine. The usual dose is 1.2 to 1.8 g daily in divided doses, which can be increased to 2.4 g. Ibuprofen is of low toxicity in acute overdose, and symptoms are unlikely even after ingestion of 100 mg/kg (Court et al 1983, Smolinske et al 1990). Life-threatening symptoms are usually not seen before 400 mg/kg or more has been ingested (Smolinske et al 1990), and even then fatal outcome is more likely due to co-ingestants (Hall et al 1992). The most common symptoms are mild gastrointestinal disturbances or minor CNS depression and dizziness. More serious symptoms include shock, coma, and metabolic acidosis (Zuckerman and Uy 1995).

Treatment of ibuprofen overdose is mostly supportive, but activated charcoal, gastric lavage, and ipecac syrup have all been used (Hall et al 1992), though the effect of activated charcoal on absorption of ibuprofen has not been studied.

### 4.5. Moclobemide

Moclobemide is a selective and reversible inhibitor of monoamine oxidase type A (MAO-A). The absorption of moclobemide is rapid after oral dosing, and its bioavailability is 90% in continuous use. Mean peak plasma concentrations are obtained at 1 to 2 h (Raaflaub et al 1984). Moclobemide is poorly bound to plasma proteins (Mayersohn and Guentert 1995) and is eliminated almost entirely by the liver; less than 0.5% of the parent compound is excreted unchanged in the urine (Jauch et al 1990).

Therapeutic indications for moclobemide are major depression and severe social phobias. The recommended initial dose is 300 mg daily either once or in divided doses; dose can be increased to 600 mg. The $C_{max}$ and AUC of moclobemide increase significantly during continuous use in the first week because of the saturation of its first-pass metabolism (Schoerlin et al 1987). Following the administration of one dose of 50 to 300 mg, the plasma concentrations were 0.3 to 2.7 mg/l (Raaflaub et al 1984). Moclobemide alone is a rather non-toxic compound, and no fatalities have occurred even after ingestion of 21 g (Dollery 1999) and with plasma concentrations 10 to 30 times the therapeutic level (Iwersen and Schmoldt 1996). Patients either had no symptoms or mild and reversible central nervous system or gastrointestinal symptoms. The seriousness of moclobemide overdose is determined by any other agents ingested at the same time, and deaths have been reported (Hilton et al 1995). Fatal serotonin syndrome has followed combination of moclobemide with the selective serotonin re-uptake inhibitor citalopram or with the tricyclic antidepressant clomipramine (Neuvonen et al 1993).

Management of a pure moclobemide overdose is symptomatic, and common gastric decontamination procedures can be used. However, the effect of activated charcoal on moclobemide absorption has not been studied. Overdose cases with other agents are treated depending on these agents. Serotonin syndrome needs aggressive treatment due to its rapid progression.

### 4.6. Temazepam

Temazepam is a short-acting benzodiazepine with pharmacological activity similar to that of oxazepam and diazepam, such as central nervous system sedation. With the formulations containing a solution of the drug in polyethylene glycerol, absorption is rapid and bioavailability is around 100%. $C_{max}$ is seen in less than 1 h, and 80% of the peak value is reached even before 20 minutes (Fuccella et al 1977, Fuccella 1979). Temazepam is highly bound to plasma proteins, with the free fraction only 2 to 4% (Divoll et al 1981b). It is metabolised in the liver mainly by conjugation with glucuronic acid to inactive metabolites (Schwarz 1979). The conjugates are mainly (80%) excreted in the urine (Dollery 1991).

Temazepam is clinically useful for short-term treatment of insomnia and as premedication before minor surgery. The usual dose before sleeping is 10 to 30 mg and 20 to 40 mg before surgery. The mean $C_{max}$ after a dose of 20 mg is 660 to 1100 μg/l. Temazepam, like diazepam, is fairly non-toxic, but fatal overdose cases have also been reported (Martin and Chan 1986). Buckley et al (1995) assessed the relative toxicity and sedative effects of benzodiazepines, finding all benzodiazepines to be quite safe, but temazepam to be more sedative than the others. The most prominent symptom in acute overdose is thus drowsiness.

Treatment of temazepam poisoning consists of general supportive measures and gastric decontamination procedures. Gastric lavage and activated charcoal are both used, but the effect of charcoal on the absorption or elimination of temazepam has not been studied.

### 4.7. Theophylline

Theophylline is a naturally occurring alkaloid found in the leaves of *Camellia sinensis*, widely used for making tea (Dollery 1991). Theophylline is well absorbed from the gastrointestinal tract with an bioavailability of 90 to 100%. The $t_{max}$ is at 1 to 2 h with oral liquid preparations and 4 to 6 h with sustained-release formulations. The rate is

decreased by food, but the gastric contents do not have an effect on the completeness of absorption. Theophylline is about 60% bound to plasma proteins and is extensively metabolised in the liver. Many factors affect this hepatic metabolism and clearance of theophylline. Liver cirrhosis reduces clearance (Staib et al 1980), and severe congestive heart failure and cor pulmonale may reduce 40 to 70% of theophylline clearance (Jusko and Eaton 1982). Ordinary formulations have a relatively short plasma half-life, and their plasma drug concentrations vary greatly. Thus to avoid serious side-effects, many sustained-release formulations of theophylline are in general use.

Theophylline is used for the treatment of asthma and chronic obstructive lung disease. The usual starting dose is 300 mg twice daily, but the dose must be individually titrated and depends on the patient as well as on the disease severity. The desired plasma concentration is 5 to 15 mg/l. Theophylline is a complex drug, since the plasma concentration must be high enough to be potent, but large doses are life-threatening. The correlation between seizure induction and theophylline plasma concentration is, however, not very close but dependent also upon the patient's age. Seizure frequency increases after concentrations greater than 50 mg/l, but young patients do not usually develop serious problems with a plasma concentration less than 80 to 100 mg/l (Kelly 1987). The main symptoms of theophylline overdose are nausea, vomiting, gastrointestinal bleeding, metabolic acidosis, hypokalaemia, rhabdomyolysis, hypotension, cardiac arrhythmia, and seizures. The mortality rate associated with theophylline-induced seizures has been high (29%) and appears to be dependent on patient age (Kelly 1987). Cardiac arrhythmia, such as ventricular tachycardia, is also often fatal.

Activated charcoal effectively reduces theophylline absorption (Sintek et al 1979, Neuvonen et al 1983b), and at low doses of ingested theophylline, charcoal alone is sufficient. (Gastric lavage seems to offer no additional benefit, according to Minton et al, 1995). Charcoal should be given in repeated doses in the case of any slow-release formulation. Goldberg et al (1987) showed that in healthy volunteers, multiple dose charcoal reduced the AUC of slow-release theophylline by 63%. They did not mention whether the $T_{1/2}$ changed, but the reduction was probably due both to inhibition of

absorption and to enhancement of theophylline clearance. If the amount of ingested theophylline has been large, especially if the plasma concentration is over 100 mg/l or is still increasing, haemoperfusion or haemodialysis should be added to the treatment. Haemoperfusion has been recommended as more effective, and haemodialysis has been considered to be inefficient (Jenne 1984). In the study of Shannon (1997) haemodialysis, however, appeared to be as effective as haemoperfusion and showed a lower rate of procedural complications.

### 4.8. Verapamil

Verapamil is a calcium-channel blocker which is over 90% absorbed after oral administration, but due to its extensive first-pass metabolism in the liver its bioavailability is only about 20% (Henry 1980). The $C_{max}$ is attained 1 to 2 h after oral administration of a conventional tablet and between 4 and 8 h after sustained-release formulations. Verapamil is extensively (90%) bound to plasma proteins, mainly to albumin.

The main therapeutic indications for verapamil are hypertension and supraventricular arrhythmia. Usual doses vary from 120 to 480 mg daily in divided doses for standard formulations; with the sustained-release tablets, that dose is given once or twice daily. Verapamil is a toxic compound in high doses, and irrespective of treatment some overdose cases still have a fatal outcome. The usual symptoms in overdose are hypotension, bradycardia, and atrioventricular block. The $C_{max}$ is about 30 μg/l after a single 80 mg dose and about 110 μg/l after three weeks of 80 mg three times daily (Dollery 1991). In patients with verapamil poisoning, the highest concentration known to be survived was 4.0 mg/l (Hofer et al 1993), whereas in fatal cases the concentration has ranged from 700 μg/l to 9.3 mg/l. In one case report (Ashraf et al 1995), a patient had taken 24 g of slow-release verapamil, and still survived, while in another study the highest dose ingested with survival was 8 g (Hofer et al 1993).

Management of verapamil poisoning consists of calcium, which can be classified as an antidote against all calcium-channel blockers, and of symptomatic supportive measures.

Activated charcoal reduces the absorption of verapamil effectively when administered immediately after drug ingestion. Later on, the efficacy of charcoal is dependent on the formulation of the drug. Two hours after ingestion of the ordinary formulation, no significant change has been observed, whereas the absorption of sustained-release formulation was reduced by charcoal by 35% (Laine et al 1997c).

## AIMS OF THE STUDY

The purpose of these studies was to evaluate the current epidemiology of acute adult poisonings in Finland and to compare in experimental studies with healthy volunteers the efficacies of the gastrointestinal decontamination methods currently used in acute drug poisonings.

The specific aims were as follows:

1. To study the epidemiology of acute poisonings in adults at the end of the twentieth century by using a cohort of patients from one hospital (I)

2. To assess the reliability of medical history taken from patients with an acute drug overdose (II)

3. To study the efficacy of activated charcoal in the absorption of citalopram, diazepam, ibuprofen, moclobemide, and temazepam (III, IV)

4. To compare the efficacy of activated charcoal alone, gastric lavage alone, and charcoal preceded by lavage in preventing the absorption of diazepam, ibuprofen, citalopram, moclobemide, temazepam, and verapamil either immediately or half an hour after ingestion (III, IV, V)

5. To compare the efficacy of activated charcoal alone and charcoal followed by whole-bowel irrigation in preventing the absorption of slow-release formulations of carbamazepine, theophylline, and verapamil 1 h after ingestion (VI)

## MATERIALS AND METHODS

### 1. SUBJECTS

Studies I and II were performed on acutely poisoned patients attending the emergency department of Meilahti Hospital (part of the Helsinki University Central Hospital) and Studies III to VI on healthy volunteers. In Study I all adult patients presenting with any acute poisoning during one month were included (226), whereas in Study II only those patients with drug poisonings were included in one month (51). These study months were not the same.

Altogether 36 healthy volunteers took part in the Studies III to VI. None of them was on continuous medication except for 12 female subjects who were using contraceptive steroids. The subjects were ascertained to be healthy by a medical history, a physical examination, and routine laboratory tests [Hb (Hemoglobin), ALT (Alanine Aminotransferase), ALP (Alkaline phosphatase), γ-GT (γ-Glutamyltransferase), hCG (human chorionic gonadotropin), plus K (Potassium), Na (Sodium), Crea (creatinine) in some of the studies] before they entered the study.

**Table 1.** Characteristics of the subjects

| Study No. | No of subjects (female/male) | Age (y) (mean with range) | Weight (kg) (mean with range) | Height (cm) (mean with range) | No using oral contraceptives |
|---|---|---|---|---|---|
| **I** | 226 (113/113) | NA | NA | NA | NA |
| **II** | 51 | NA | NA | NA | NA |
| **III** | 9 (7/2) | 24 (19-40) | 69 (56-87) | 173 (158-187) | 4 |
| **IV** | 9 (5/4) | 23 (19-33) | 66 (55-88) | 172 (163-187) | 1 |
| **V** | 9 (5/4) | 26 (21-32) | 64 (51-89) | 169 (154189) | 3 |
| **VI** | 9 (5/4) | 24 (20-39) | 70 (53-100) | 169 (159-183) | 4 |

## 2. STUDY PROTOCOLS

### 2.1. Study designs

**Study I** Epidemiology of acute poisonings was followed in a prospective study including all the 226 patients with acute poisoning with drugs, alcohol, or other toxic products who arrived at the Meilahti Hospital during May, 1997. The study protocol involved 20 variables to characterise the patient population. Systematic information was obtained by interviewing the patients and/or the accompanying persons as well as collecting the details from the medical records. Each patient's data were recorded on a standard data collection sheet designed specifically for this study.

**Study II** In this prospective study, 51 patients with acute drug poisoning took part. The patients and/or their accompanying persons were interviewed on admission to gain systematic information about the drugs or other toxic agents taken. Blood, urine, and/or gastric lavage samples were also taken on admission. The samples were then analysed in the Department of Forensic Medicine (University of Helsinki) and the results compared with those gained by the interviews or companions.

**Studies III to VI** used a randomised, placebo-controlled, cross-over study design in three phases with a suitable wash-out interval. The volunteers fasted for at least 8 hours before administration of study drugs and ate a light standard meal 3 and 7 hours afterwards. Alcohol, coffee, tea, or cola were forbidden during the study days.
The activated charcoal used in these studies was given as a suspension in 200 ml of water. It was prepared by shaking the charcoal with tap water just before use.

**Table 2**: Structure of Studies III to VI

| Study No. | Drugs | Treatments | Time interval between drug administration and gastric decontamination |
|---|---|---|---|
| **III** | diazepam 5 mg<br>ibuprofen 400 mg<br>citalopram 20 mg | 1. activated charcoal<br>2. gastric lavage followed by charcoal | 30 min |
| **IV** | moclobemide 150 mg<br>temazepam 10 mg<br>verapamil 80 mg | 1. activated charcoal<br>2. gastric lavage | 5 min |
| **V** | moclobemide 150 mg<br>temazepam 10 mg<br>verapamil 80 mg | 1. activated charcoal<br>2. gastric lavage | 30 min |
| **VI *** | carbamazepine 200 mg<br>theophylline 200 mg<br>verapamil 120 mg | 1. activated charcoal<br>2. whole-bowel irrigation preceded by charcoal | 1 h |

***** In Study VI all the drugs were sustained-release formulations

**Study III** Nine volunteers (7 women and 2 men) each were given 5 mg diazepam (Stesolid®, Dumex-Alpharma, Denmark), 400 mg ibuprofen (Brufen®, Knoll AG, Germany), and 20 mg citalopram (Cipramil®, Lundbeck, Denmark) simultaneously with 150 ml water at 8.30 h. Thirty minutes afterwards, these subjects were assigned to one of the following treatments: 1) 200 ml water (control), 2) 25 g activated charcoal (Carbomix®, Leiras, Finland) as a suspension in 200 ml water, or 3) gastric lavage, followed by 25 g charcoal in suspension given through the lavage tube. Blood samples to determine plasma concentrations of diazepam, ibuprofen, and citalopram were drawn immediately before drug administration and 0.5, 1, 1.5, 2, 3, 5, 7, and 10 h later. Although the $T_{1/2}$ of citalopram is about 36 h and that of diazepam 20 to 100 h, the follow-up time was considered to be sufficiently long, since the possible differences between treatments were already evident during these 10 h. Plasma was separated within 30 min, divided into three tubes, and stored at -20°C until analysis.

**Study IV** Nine volunteers (5 women, 4 men) each received 10 mg temazepam (Normison®, Wyeth-Pharma, Germany), 80 mg verapamil (Verpamil®, Orion Pharma, Finland), and 150 mg moclobemide (Aurorix®, F.Hoffman-La Roche, Switzerland)

simultaneously with 150 ml water at 8.30 h. Five minutes afterwards, these subjects were assigned to one of the following treatments: 1) 200 ml water (control), 2) 25 g activated charcoal (Carbomix®, Leiras, Finland) as a suspension in 200 ml water, or 3) gastric lavage. Blood samples to determine plasma concentrations of temazepam, verapamil, and moclobemide were drawn immediately before drug administration and 0.5, 1, 1.5, 2, 3, 5, 7, 10, and 24 h later. Follow-up time was lengthened to 24 h in Studies IV to VI in order to avoid any possible source of error when calculating AUCs. Plasma was separated within 30 min, divided into three tubes, and stored at -20°C until analysis. Urine was collected cumulatively in fractions at 1 to 10 h and 10 to 24 h. The total volume of each fraction was measured, and a 10 ml sample was taken for analysis. The samples were stored at -20°C until analysed.

**Study V** Nine volunteers (5 women, 4 men) each received 10 mg temazepam (Normison®, Wyeth-Pharma, Germany), 80 mg verapamil (Verpamil®, Orion Pharma, Finland), and 150 mg moclobemide (Aurorix®, F.Hoffman-La Roche, Switzerland) simultaneously with 150 ml water at 8.30 h. Thirty minutes afterwards, these subjects were assigned to one of the following treatments: 1) 200 ml water (control), 2) 25 g activated charcoal (Carbomix®, Leiras, Finland) as a suspension in 200 ml water, or 3) gastric lavage. Blood samples to determine plasma concentrations of temazepam, verapamil, and moclobemide were drawn immediately before drug administration and 0.5, 1, 1.5, 2, 3, 5, 7, 10, and 24 h later. Plasma was separated within 30 min, divided into three tubes, and stored at -20°C until analysis.

**Study VI** Nine volunteers (5 women, 4 men) each received 200 mg theophylline (Theo-Dur depottablet®, Finnish Astra OY, Finland), 120 mg verapamil (Isoptin retard®, Knoll AG, Germany), and 200 mg carbamazepine (Tegretol retard®, Novartis Finland OY, Finland) simultaneously with 150 ml water at 8.00 h. One hour afterwards, these subjects were assigned to one of the following treatments: 1) 200 ml water (control), 2) 25 g activated charcoal (Carbomix®, Leiras, Finland) as a suspension in 200 ml water, or 3) 25 g activated charcoal as a suspension, followed by whole-bowel irrigation. Blood samples to determine plasma concentrations of theophylline, verapamil, and carbamazepine were drawn immediately before drug administration and 1, 2, 3, 4, 5, 6,

8, 10, and 24 h later. Plasma was separated within 30 min, divided into three tubes and stored at -70°C until analysis.

### 2.2. Concomitant treatment

Volunteers in Studies III to VI were not allowed to use any regular medication during the studies except oral contraceptive (OC) pills, which were used by 4 women (III), 1 (IV), 3 (V), and 4 (VI). Although etinylestradiol is known to inhibit some cytochrome P450 enzymes such as 1A2, 3A4, and possibly also 2C19, we did not consider this a problem, since every subject was also her own control, and any possible interaction with study drugs would occur in every study phase. All users had also used OCs for several months, which minimised the differences between levels of etinylestradiol during their cycles.

Since our gastric decontamination methods would also have prevented the absorption of an OC pill had it been taken just before the procedures, all subjects were instructed to take their pills only in the evenings.

### 2.3. Determination of plasma and urine drug concentrations

Samples from Study II were analysed in the Department of Forensic Medicine (University of Helsinki). All other plasma and urine drug concentrations (Studies III-VI) were determined in the Analytical Laboratory of the Department of Clinical Pharmacology, University of Helsinki.

**Study II** Serum samples were analysed for drugs by dual channel gas chromatographic methods, using appropriate internal standards. Acidic and neutral drugs were extracted together from 1 ml serum at pH 7.4 with 500 µl ethyl acetate. Two Micromat HRGC 412 gas chromatographs, one with an electron capture detector and one with a nitrogen-phosporus detector, were used for analysis. Basic drugs were extracted from 1 ml serum at pH 9.3 with 300µl butyl acetate. A Micromat HRGC 412 gas chromatograph with a nitrogen-phosphorus detector was used for analysis (Rasanen 1996).

Thin layer chromatography was used for analysis of drugs in urine samples. Acidic drugs were extracted with diethyl ether at pH 3 from a 5-ml sample of urine. For extraction of basic drugs, the water layer was buffered to pH 7.5, and the drugs were separated as ion pairs with a hydrophobic counter-ion with dichloromethane (Ojanperä 1996).

Because of high concentrations of drugs, gastric samples were spotted directly on the plates.

**Study III** Plasma concentrations of diazepam were determined by gas chromatography using methoxydiazepam as an internal standard (Gaillard et al. 1993). The quantification limit was 0.5 ng/ml, and the between-day CVs were 3.2% (at 0.97 ng/ ml, n=6) and 1.9% (at 97.8 ng/ml, n=6). Concentrations of ibuprofen were measured by HPLC, with indomethacin as the internal standard (Sochor et al. 1995). The quantification limit was 0.5 mg/l, and the between-day CVs were 8.0% (at 0.97 mg/l, n=12) and 3.4% (at 15.5 mg/l, n=12). Plasma concentrations of citalopram were determined by gas chromatography, with amitriptyline as the internal standard (Reymond et al. 1993). The quantification limit was 1.0 ng/ml and the between-day CVs were 5.5% (at 2.6 ng/ml, n=6) and 2.2% (at 10.4 ng/ml, n=5).

**Study IV** Plasma and urine temazepam concentrations were determined by HPLC, with methoxydiazepam as the internal standard (Rao et al. 1982). The quantification limit was 5 ng/ml, and the between-day CV for plasma temazepam was 10.0% at 98.5 ng/ml (n=9) and for urine temazepam 23% at 295 ng/ml (n=10). Plasma and urine concentrations of verapamil were determined by HPLC with methoxyverapamil as the internal standard (Hynning et al. 1988). The limit of quantification was 1 ng/ml, and the between-day CV for verapamil was 2.3% at 19.57 ng/ml (n=9) for plasma and 5.5% at 19.7 ng/ml (n=3) for urine. HPLC was used to determine plasma concentrations of moclobemide (Raaflaub et al. 1984, Geschke et al. 1987), with lidocaine as the internal standard. The limit of quantification for moclobemide concentrations was 5 ng/ml, and the between-day CV 6.1% at 152 ng/ml (n=9) for plasma and 0.5% at 150 ng/ml (n=2) for urine.

**Study V** HPLC was used to determine the plasma concentrations of moclobemide (Raaflaub et al. 1984, Geschke et al. 1987), with lidocaine as the internal standard. The limit of quantification was 5 ng/ml, and the between-day CVs were 3.2% at 829 ng/ml (n=11) and 10.9% at 14 ng/ml (n=11). Plasma concentrations of temazepam were determined by HPLC with methoxydiazepam as the internal standard (Rao et al. 1982). The limit of quantification was 5 ng/ml, and the between-day CVs were 6.4% at 279 ng/ml (n=10) and 9.1% at 16.7 ng/ml (n=10). Concentrations of verapamil in plasma were also determined by HPLC, with methoxyverapamil as the internal standard (Hynning et al. 1988). The limit of quantification was 2 ng/ml, and the between-day CVs were 6.6% at 174 ng/ml (n=10) and 13.4% at 1.87 ng/ml (n=10).

**Study VI** Plasma concentrations of carbamazepine in plasma were determined by HPLC, with cyheptamide as the internal standard (Hartley et al 1986). The limit of quantification was10 ng/ml, and the between-day CVs were 4.8% at 46.9 ng/ml and 2.9% at 1919.7 ng/ml (n=6 for both concentration levels). Plasma theophylline concentrations were determined by HPLC, with betahydroxyethyltheophylline as the internal standard (Pickard et al 1986). The limit of quantification was 2.0 ng/ml, and the between-day CV was 2.8% at 150 ng/ml (n=9) and 2.6% at 3971 ng/ml (n=8). Plasma verapamil concentrations were determined by HPLC, with methoxyverapamil as the internal standard (Hynning et al 1988). The limit of quantification was 2 ng/ml, and the between-day CVs were 3.0% at 158.2 ng/ml (n=10) and 11.0% at 3.1 ng/ml (n=9).

### 2.4. Pharmacokinetic calculations

The absorption of study drugs was characterised by use of the area under the plasma concentration-time curve from 0 to t hours [AUC(0-t)], calculated by the linear trapezoidal method, peak plasma concentration ($C_{max}$), and time to peak ($t_{max}$). The $C_{max}$ and $t_{max}$ were taken directly from the data. In some studies, a variable, $C_{\Delta}$ , was calculated to characterise the effect of the treatments on absorption of the drugs from the treatment-point onwards. $C_{\Delta}$ was $C_{max}$ minus $C_{tp}$. However, if the $C_{max}$ had already occurred when the treatment was started, then, during the treatment phase $C_{\Delta}$ was equal to $C_{max}$ minus the concentration measured at the $t_{max}$ of the control (water) phase. In

Study V, urine was collected in fractions at 0-10 h and 10-24 h, but the final results were cumulative excretion over 24 h.

### 2.5. Activated charcoal, gastric lavage, and whole-bowel irrigation

The activated charcoal used in our Studies III to VI was Carbomix® granules (Leiras Oy, Turku, Finland). The oral suspension was prepared by adding water to Carbomix® just before giving it to the subjects. The tendency of Carbomix® to separate into two phases (in water) was prevented by stirring the suspension even while using it. Carbomix® has a surface area of $2000 m^2/g$.

Gastric lavage was performed with the subject in a sitting position, though there are also many studies where patients or volunteers have been placed in the left lateral position with the head lowered 10 degrees. This position is thought to minimize loss of gastric contents into the small bowel but it is uncomfortable for the patient, and its efficacy is not clearly shown (Burke 1972). Therefore we used the routine position for clinical use in Finland. A standard large-bore orogastric tube was used, length 80 cm, inner diameter 8 mm, and outer diameter 10 mm. Two nurses with long experience in performing gastric lavage on intoxicated patients carried out the procedure. Lavage was with two litres of warm tap water in repeated 200 ml aliquots.

Whole-bowel irrigation was carried out by having each subject drink PEG solution (Colonsteril, Orion Pharma, Finland) at a rate of one l/h until the stools produced were coloured with activated charcoal. The PEG solution was kept at room temperature in order to avoid possible hypothermia.

### 2.6. Statistical methods

**Study I** In this epidemiological study, the characteristics of variables were partly descriptive, and no statistical methods were used for them. Differences between men and women in the number of poisonings occurring in specific age-groups and in the types of toxic agents involved were analysed by calculating the 95% confidence interval

for the expected ratio of men to women (1:1). P values <0.05 were considered statistically significant.

**Study II** contained only descriptive data.

**Studies III to VI** Results are expressed as mean values with standard deviations (SD) or, in the case of $t_{max}$, as median with range, with 95% confidence intervals (CI) calculated for selected variables. One-way analysis of variance (ANOVA), with the Tukey test used for post hoc comparisons, served for statistical analysis of the results, except for $t_{max}$ data which were analysed by the Wilcoxon test. A paired t-test (two-tailed) served as an alternative statistical method in some cases to check the results, but there was no contradiction between these tests. The power of the studies to detect a 30% difference in AUC(0-t) between two treatments was about 80% at the 5% level of significance. The level of statistical significance was $P<0.05$. The statistical analysis was done by Systat for Windows, version 6.0 (SPSS Inc., Chicago, IL, USA).

### 2.7. Ethical considerations

The protocols of Studies I and II were approved by the Ethics Committee of the Department of Internal Medicine, Meilahti Hospital of Helsinki University Central Hospital. The protocols of Studies III to V were approved by the Ethics Committee of the Department of Clinical Pharmacology, University of Helsinki, and Study VI by the Ethics Committee for Studies in Healthy Subjects of the Hospital District of Helsinki and Uusimaa. All these ethics committees included both medical and lay members as currently required. The protocols of Studies III to VI were also sent to the Finnish National Agency for Medicines for evaluation, and the Declaration of Helsinki was followed in all studies. Oral informed consent was obtained from the patients in the Studies I and II and written informed consent from each volunteer prior to Studies III to VI.

## RESULTS

### 1. EPIDEMIOLOGY OF ACUTE POISONINGS

During the study month of Study I, acute poisonings comprised 15% of those admissions which concerned the speciality of internal medicine. Gender numbers were equal (113 men and 113 women), though the highest number of poisonings occurred in men in the age-group 28 to 37 years and in women 38 to 47. In the age-groups 18 to 27 and 28 to 37, poisonings were more common in men, whereas in age-groups 38 to 47 and 48 to 57, more common in women. The difference was, however, statistically significant ($P<0.05$) only for age-group 48 to 57 years. Ten patients presented more than once, and six cases (2.7%) were considered accidental poisonings.

In Study I, most cases of poisoning in both men (66%) and women (67%) involved alcohol (Table 3), with alcohol the sole poison in 24% and 11% of men and of women. Among drugs, psychotropic agents predominated in both genders, anxiolytes (mostly benzodiazepines) being most often involved. Benzodiazepine derivatives were the most common drugs also when history was confirmed by drug analyses; analyses also showed that the majority of patients in that study group had taken both ethanol and drugs (55%). Comparison between the genders showed that antidepressants and NSAIDs were significantly ($P<0.05$) more often used by women, whereas ethanol alone and illicit drugs significantly ($P<0.05$) more common with men. Concomitant intake of drugs and alcohol was common in most age-groups in both genders, but in young men (18-27) illicit drugs already were appearing more often than only drugs or only alcohol.

**Table 3**: Toxic agents involved in the study I

| Agent | Men | Women | Total |
|---|---|---|---|
| Ethanol involved | 75 | 76 | 151 |
| Anxiolytics | 41 | 57 | 98 |
| (benzodiazepines) | (36) | (52) | (88) |
| Neuroleptics | 26 | 16 | 42 |
| Ethanol alone | 27 | 12* | 39 |
| Antidepressants | 13 | 25* | 38 |
| Zopiclone or zolpidem | 13 | 24 | 37 |
| NSAIDs | 1 | 14* | 15 |
| (including aspirin) | | | |
| Illicit drugs | 12 | 2* | 14 |
| Antiepileptics | 8 | 5 | 13 |
| Paracetamol | 2 | 7 | 9 |
| Antihistamines | 1 | 6 | 7 |
| Opioids | 3 | 2 | 5 |
| Orphenadrine | 0 | 4 | 4 |
| Ethylene glycol | 3 | 0 | 3 |
| Lithium | 0 | 3 | 3 |
| Carbon monoxide | 2 | 1 | 3 |
| Others | 2 | 6 | 8 |

* Significantly different from men

The presentation of patients to the emergency department showed clear circadian variation, the busiest time being between 7 p.m. and 9 p.m, and the most quiet time between 8 a.m. and 10 a.m. Presentation time does not directly indicate when the poisonous agents had been taken, however, since only 9% of cases presented within 1 h and 24% within 2 h of ingestion of the poison. In two-thirds of the cases, the delay in presentation exceeded 4 h.

The clinical status of the patients on arrival was generally good in both cohorts, though the number of serious cases was more prominent in the later study (II; 6% vs. 15%). Activated charcoal was the most common treatment. Sixty percent of patients received at least one 50-g dose of charcoal, and in cases of drug poisoning, over 80% received charcoal. The reasons for omitting charcoal in 20% of the patients were the small amount of poison or the patient's having initially been treated elsewhere and receiving charcoal there. Gastric lavage was performed in half the cases, and 15% underwent whole-bowel irrigation. Antidotes were given in special cases, mostly flumazenil against benzodiazepines. Haemodialysis or haemoperfusion were used four times for carbamazepine, lithium, and acetosalisylic acid. There were no fatal cases in either study. The longest duration of hospital stay was 11 days (a case involving verapamil), but 94% of patients were discharged from the hospital within 24 h.

## 2. RELIABILITY OF THE MEDICAL HISTORY

The study period of Study II was one month, and patients with apparent ethanol intoxication were excluded. However, the majority of the rest of the patients had in fact taken alcohol, with serum ethanol concentration of 0.5 g/l or higher found in 55% of these patients. Three patients were excluded later since their diagnosis appeared to be something other than poisoning, and one patient left before any tests were taken. Thus, 51 patients supplied data for this study.

A serum sample was taken from 84% of these 51 patients, gastric lavage fluid from 41%, and a urine sample from 22%. Information obtained on admission completely agreed with the toxicologic analyses in only 27% of the cases. In 55% of the cases, however, the discrepancy was only minor and was of no clinical importance. However, in 9 cases the history was seriously misleading. A life-threatening overdose, like lithium or dextropropoxyphene, was suspected in 6 patients because of the history but 4/6 had taken other drugs, and 2 had actually taken nothing at all. In contrast 3 patients denied either wholly or in part any drug ingestion, but their laboratory samples revealed one severe chlordiazepoxide poisoning, one triazolam poisoning, and one poisoning with

dextropropoxyphene and paracetamol. Although these discrepancies were considered clinically important, they did not cause these patients any complications.

## 3. EFFECT OF ACTIVATED CHARCOAL ON DRUG ABSORPTION

Effect of activated charcoal on preventing the absorption of drugs was studied both alone and preceded by gastric lavage or followed by whole-bowel irrigation. Results of combination treatments are presented more specifically in the sections on gastric lavage and whole-bowel irrigation.

### 3.1. Effect of charcoal on ordinary formulations of drugs

The effect of activated charcoal was studied immediately (5 min) (Study IV) or 30 min (Study V) after the ingestion of ordinary drugs. When charcoal was given immediately after ingestion, it reduced the AUC(0-24) of temazepam by 95% ($P<0.01$) compared with the control (Figure 1). The $C_{max}$ of temazepam was also reduced by 95% ($P<0.01$). Charcoal also reduced the 24-hour cumulative excretion of temazepam into the urine by 71% ($P<0.05$). As for verapamil, its AUC(0-24) was reduced by 93% ($P<0.01$) (Figure 1), and $C_{max}$ was reduced by 94%, ($P<0.01$). The 24-hour cumulative excretion of verapamil into the urine fell by 94% ($P<0.01$). The absorption of moclobemide was prevented almost completely: The reduction of its AUC(0-24) was 99.7% ($P<0.01$) (Figure 1). Its $C_{max}$ was reduced by 99.5% ($P<0.01$). The 24-hour cumulative excretion into the urine was reduced by 99.8% ($P<0.05$) by the activated charcoal.

When charcoal was given 30 min after the ingestion of these drugs, the AUC(0-24) of moclobemide was reduced by 55% ($P<0.05$); its $C_{max}$ was reduced nonsignificantly, while reduction in the $C_{\Delta}$ was 69% ($P<0.05$). For temazepam, charcoal reduced the AUC(0-24) by 45% ($P<0.05$), and the $C_{max}$ fell by 29% ($P<0.05$), and the $C_{\Delta}$ by 93% ($P=0.06$). The AUC(0-24) of verapamil was only non-significantly reduced by activated charcoal (by 33%) (Figure 1). Reductions in the $C_{max}$ and $C_{\Delta}$ were also negligible and nonsignificant.

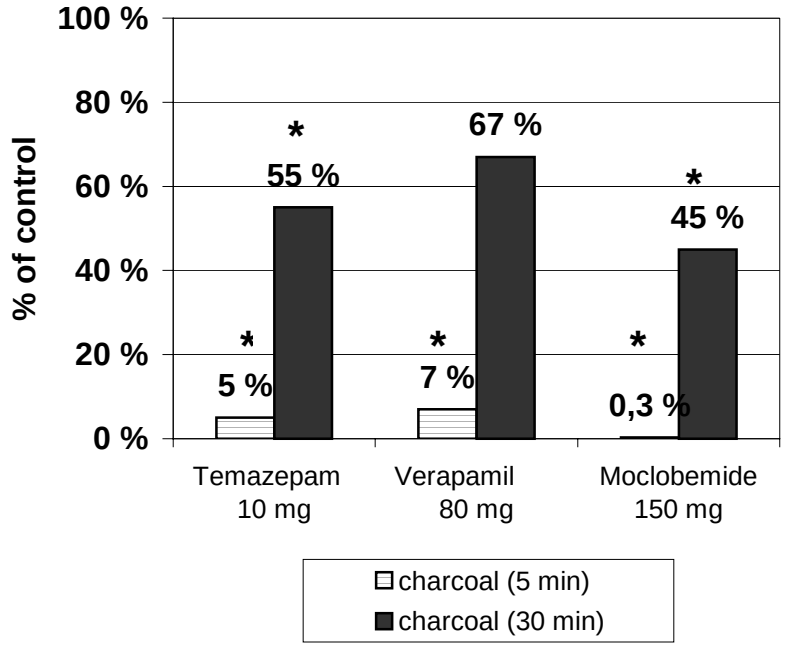


**Figure 1**: Mean AUC(0-24) of temazepam, verapamil, and moclobemide expressed as percentage of corresponding values during the control (water) phase. Activated charcoal (25g) was given 5 min (IV) or 30 min (V) after drug intake. * Significantly ($P<0.05$) diferent from control.

The effect of activated charcoal 30 min after drug ingestion, was also studied on the absorption of diazepam, ibuprofen, and citalopram (Study III). Activated charcoal alone reduced the AUC(0-10) of diazepam by 27% ($P<0.05$) and the $C_{max}$ by 17.6%. The plasma diazepam concentration continued to increase from 0.5 h onwards ($C_{\Delta}$) in the control phase, whereas charcoal prevented this increase ($P=0.05$). $C_{\Delta}$ was 28.5 ng/ml in the control phase and –7.4 ng/ml in the charcoal phase. The AUC(0-10) of ibuprofen was reduced by 30% ($P<0.05$). Charcoal was effective in preventing the increase in $C_{\Delta}$ of ibuprofen (from 17.5 µg/ml to –0.4 µg/ml, $P<0.01$), though the $C_{max}$ was reduced by

only 21%, (P=NS). The AUC(0-10) of citalopram was reduced by 51% (P<0.05). The $C_{max}$ of citalopram was reduced by 52% (P<0.05), and the $C_{\Delta}$ of citalopram was reduced to the same extent, by about 50% (Figure 2).

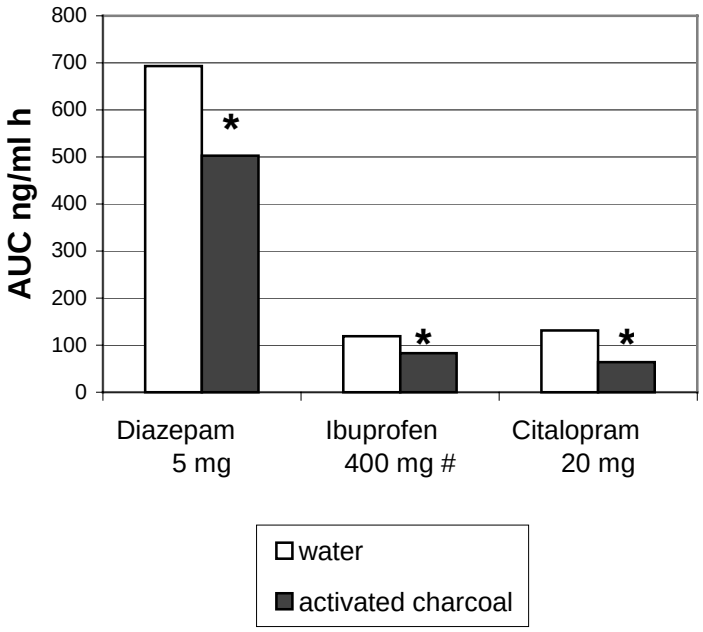


**Figure 2**: Mean AUC(0-10) of the study drugs with water or activated charcoal (25g) given 30 min after drug intake. # for ibuprofen, AUC is µg/ml h. * Significantly (P<0.05) different from control.

### 3.2. Effect of charcoal on sustained-release formulations

The sustained-release drugs used in Study VI were carbamazepine, theophylline, and verapamil, and the time-interval was one hour. Activated charcoal reduced both the AUC(0-24) and $C_{max}$ of carbamazepine by 62% ($P<0.001$) and $C_{\Delta}$ by 79% ($P<0.001$).

The AUC(0-24) of theophylline was reduced by charcoal by 75%, ($P<0.001$). The $C_{max}$ was reduced by 66% ($P<0.001$), and the $C_{\Delta}$ was reduced by 91% ($P<0.001$).

The reduction in the AUC(0-24) of verapamil was 63% ($P<0.001$). Charcoal reduced the $C_{max}$ and $C_{\Delta}$ by 57% and 61%, respectively ($P<0.01$) (Figure 3).

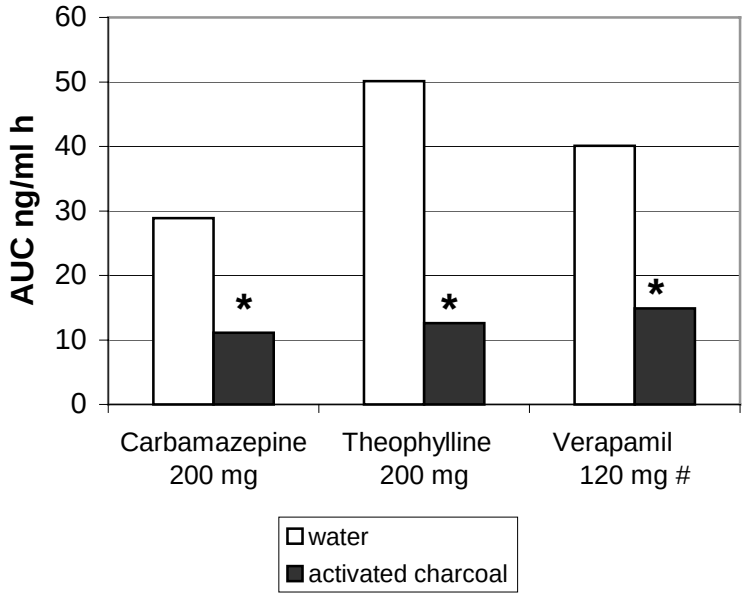


**Figure 3**: Mean AUC(0-24) of carbamazepine, theophylline, and verapamil given as sustained-release formulations. Activated charcoal (25 g) or water (control) was given one hour after drug ingestion. # for verapamil, AUC is divided by ten. * Significantly ($P<0.001$) different from control.

## 4. EFFECT OF GASTRIC LAVAGE ON DRUG ABSORPTION

### 4.1. Effect of gastric lavage alone

The effect of gastric lavage alone was studied either immediately after the ingestion of drugs (temazepam, verapamil, moclobemide) (Study IV) or half an hour after their ingestion (Study V).

Temazepam

Gastric lavage performed immediately after the ingestion of temazepam reduced the AUC(0-24) by 25.6% (P=ns) and half an hour later by 18% (P=ns) (Figure 4). The $C_{max}$ was reduced by 42.7% (P<0.01) immediately after the ingestion but only by 17% (P=ns) half an hour later. The $C_{\Delta}$ of was reduced by 89% by lavage.

The 24-hour cumulative excretion of temazepam into the urine was reduced by 14.3% (P=ns) when lavage was started immediately.

Verapamil

Gastric lavage had little effect on the AUC(0-24) of verapamil immediately after the ingestion; the reduction was 4.0% (P=ns). Half an hour later the reduction was 33%, but still the difference from the control was not significant (Figure 4). The reduction in $C_{max}$ was 7.7%, (P=ns) and 30% (P=ns), 5 min and 30 min after ingestion. The mean $C_{\Delta}$ was similar in both the control phase and the lavage phase. The 24-hour cumulative excretion of verapamil into the urine was reduced by 6.0% (P=ns).

Moclobemide

Gastric lavage reduced the AUC(0-24) of moclobemide by 32.3% (P=ns) and by 44% (P<0.05) 5 and 30 min after the ingestion (Figure 4). The $C_{max}$ was reduced by 34.6% (P=ns) compared with the control with a time-interval of 5 min. Half an hour later the reduction was 36% (P=ns), and the reduction of $C_{\Delta}$ was 17% (P=ns).

The 24-hour cumulative excretion of moclobemide into the urine was reduced by 26.7% (P=ns).

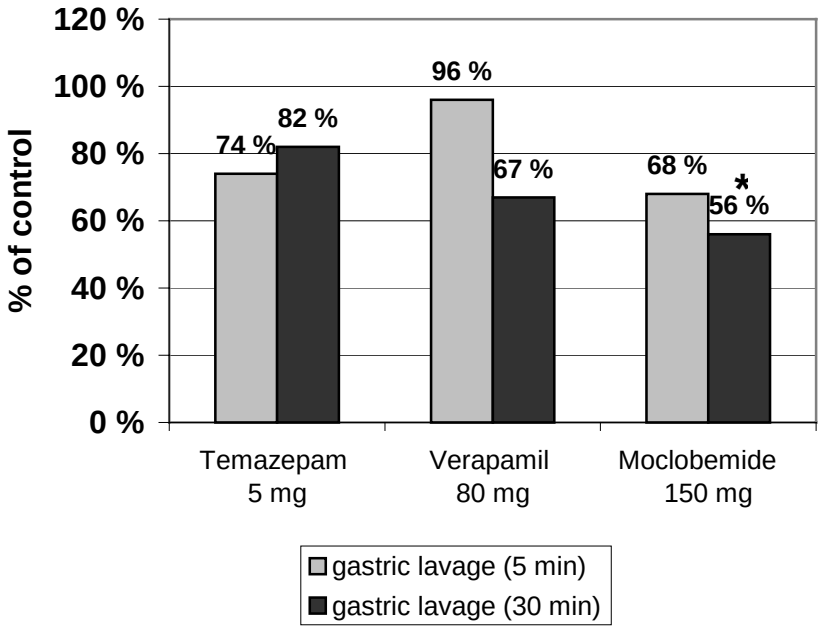


**Figure 4**: Mean AUC(0-24) of temazepam, verapamil, and moclobemide. Gastric lavage was started either 5 (IV) or 30 min (V) after drug intake, and water served as control. * Significantly ($P<0.05$) different from control.

### 4.2. Effect of gastric lavage followed by activated charcoal

Gastric lavage followed by activated charcoal reduced the AUC(0-10) of diazepam by 27% ($P<0.05$) (Figure 5) in Study III. The increase in plasma diazepam concentration from 0.5 h onwards ($C_{\Delta}$) was prevented significantly ($P<0.05$), though the change in $C_{max}$ was not significant. The AUC(0-10) of ibuprofen was reduced by 49% ($P<0.05$) (Figure 5). The $C_{max}$ of ibuprofen was reduced by 45% ($P<0.05$), and the $C_{\Delta}$ almost completely (99%, $P<0.01$). Reduction in the AUC(0-10) of citalopram was 51% ($P<0.05$) (Figure 5). The $C_{max}$ of citalopram was reduced by 54%, and the $C_{\Delta}$ was reduced to the same extent, by 53%.

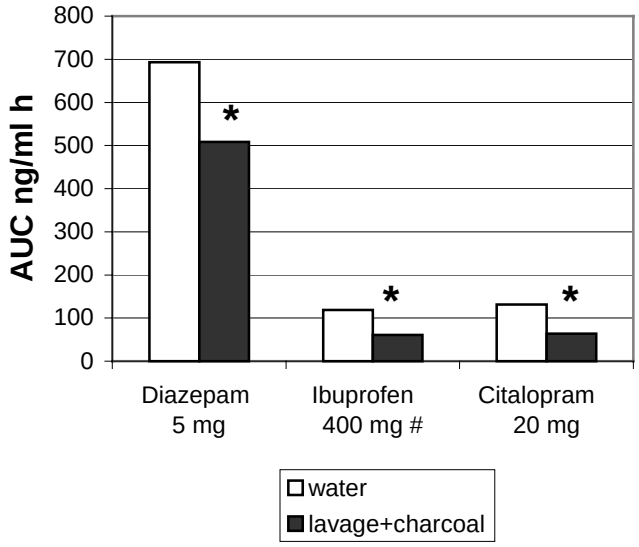


**Figure 5**: Mean AUC(0-10) of diazepam, ibuprofen, and citalopram. Activated charcoal (25g) was given after gastric lavage, with this treatment starting 30 min after drug intake. Water served as the control. # for ibuprofen, AUC is in µg/ml h. * Significantly ($P<0.05$) different from control.

## 5. EFFECT OF WHOLE-BOWEL IRRIGATION ON DRUG ABSORPTION

Effect of whole-bowel irrigation on drug absorption was studied for three sustained-release drugs, namely carbamazepine, theophylline, and verapamil (Study VI). Whole-bowel irrigation (wbi) was combined with activated charcoal (ac), which preceded it.

Combination treatment reduced both the AUC(0-24) and $C_{max}$ of carbamazepine by 41% ($P<0.01$). Reduction in $C_{\Delta}$ was 62% ($P<0.001$). The AUC(0-24) of theophylline was reduced by 65% ($P<0.001$). The $C_{max}$ of theophylline was reduced by 66% ($P<0.001$), and the $C_{\Delta}$ by 95% ($P<0.001$).The reduction in the AUC(0-24) of verapamil was 85% ($P<0.001$). The combination treatment reduced the $C_{max}$ 73% ($P<0.01$) and $C_{\Delta}$ 79% ($P<0.001$) (Figure 6).

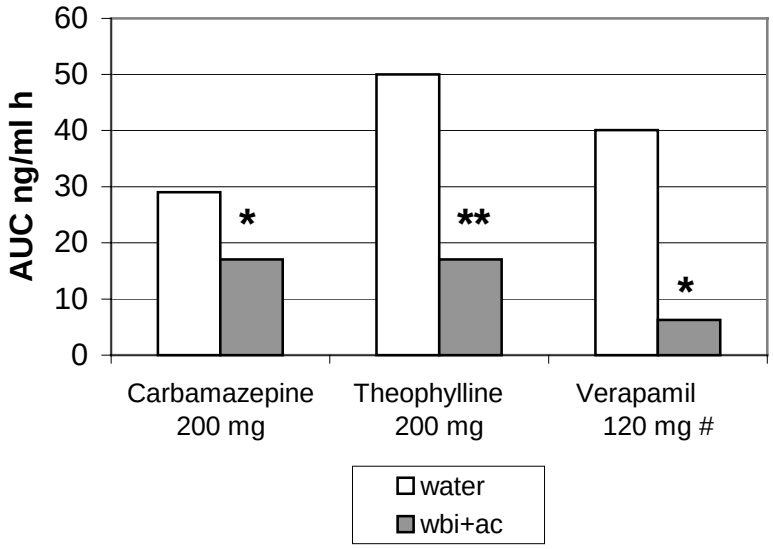


**Figure 6:** Mean AUC(0-24) of sustained-release formulations of carbamazepine, theophylline, and verapamil. Activated charcoal (ac) (25g) preceded whole-bowel irrigation (wbi), and treatment was started 1 h after drug intake. # for verapamil, AUC is divided by ten. Significantly, *($P<0.01$), **($P<0.001$) different from control.

## 6. DIFFERENCES BETWEEN TREATMENTS

### 6.1. Activated charcoal vs. gastric lavage

When gastric decontamination was performed immediately after the ingestion of drugs (temazepam, verapamil, moclobemide), gastric lavage was very inefficient in preventing the absorption compared with activated charcoal. Differences between treatments were significant for every drug.

Temazepam: The difference in AUC(0-24) between the lavage and charcoal phases was 1584 ng/ml h ($P<0.01$), and in $C_{max}$ it was 220 ng/ml ($P<0.01$) (Figure 7). The difference in reduction in the 24-hour cumulative excretion of temazepam into the urine was also significant: 12.3 μg ($P<0.05$).

Verapamil: The difference in AUC(0-24) was 198 ng/ml h ($P<0.01$) and in $C_{max}$ 33.3 ng/ml ($P<0.01$) (Figure 7). The difference in reduction in the 24-hour cumulative excretion of verapamil into the urine was also significant: 457 μg ($P<0.01$).

Moclobemide: The difference in AUC(0-24) was 3406 ng/ml h ($P<0.05$) and in $C_{max}$ 719 ng/ml ($P<0.01$) (Figure 7). The difference in the reduction in 24-hour cumulative excretion of moclobemide into the urine was also significant: 952 μg ($P<0.01$).

When the time-interval between drug administration and gastric decontamination was 30 min, differences between treatments were no longer so obvious, though gastric lavage was still less effective than charcoal.

Temazepam: The difference between the treatments in the AUC(0-24) was significant $P<0.05$ (669 ng/ml h), but reductions in $C_{max}$ or in $C\Delta$ did not significantly differ (Figure 7).

Verapamil: No significant differences existed between treatments, nor did either of them significantly differ from the control (Figure 7).

Moclobemide: No significant differences existed between treatments, but both reduced the AUC(0-24) of moclobemide significantly compared with control values (Figure 7). The treatments also reduced $C_{max}$ to the same extent; charcoal reduced the $C_{\Delta}$ of moclobemide more than did lavage, though the difference (235 ng/ml) was not quite significant (P=0.08).

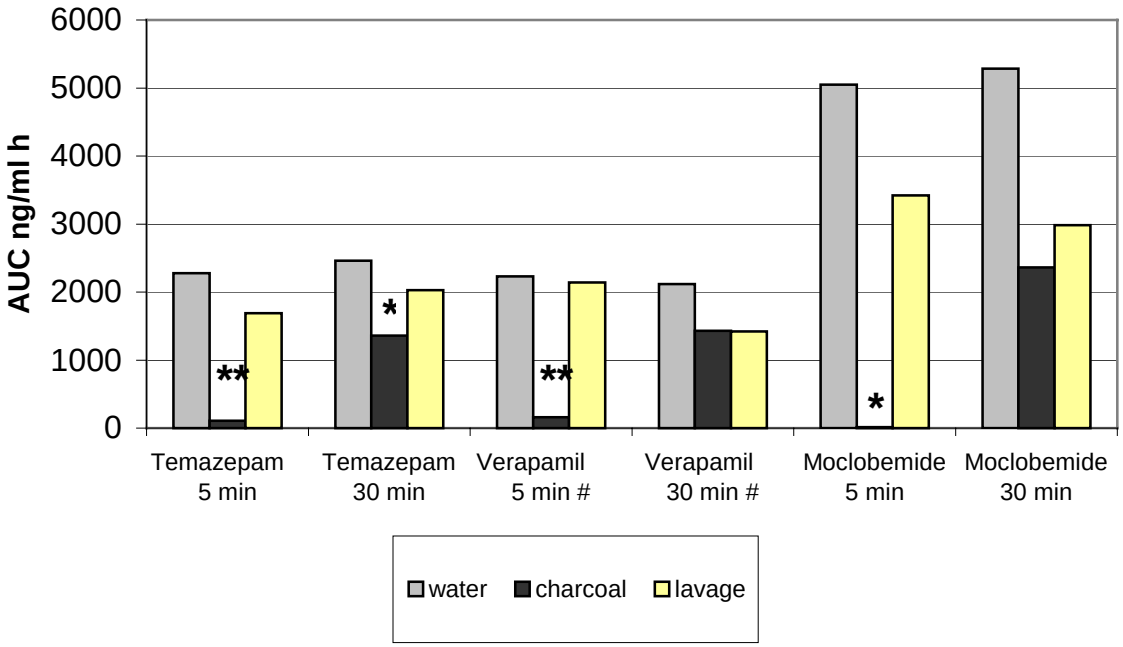


**Figure 7**: Mean AUC(0-24) of study drugs. Treatments were either activated charcoal (25 g) or gastric lavage, with water serving as the control. Treatment was started 5 or 30 min after drug intake. # AUC of verapamil multiplied by 10 for clarity. *(P<0.05), **(P<0.01) Significantly different from lavage.

### 6.2. Activated charcoal alone and preceded by gastric lavage

Both activated charcoal alone and charcoal preceded by gastric lavage reduced the absorption of drugs (diazepam, ibuprofen, citalopram) to the same extent. Thus gastric lavage brought no additional benefit, nor did it reduce the efficacy of charcoal. Both treatments reduced significantly ($P<0.05$) the AUC(0-10) of all three drugs when compared with control values (Figure 8). The effect on the $C_{max}$ of the drugs was less prominent, but both treatments prevented significantly ($P<0.05$) the further absorption of all three drugs from 0.5 h onwards ($C_{\Delta}$).

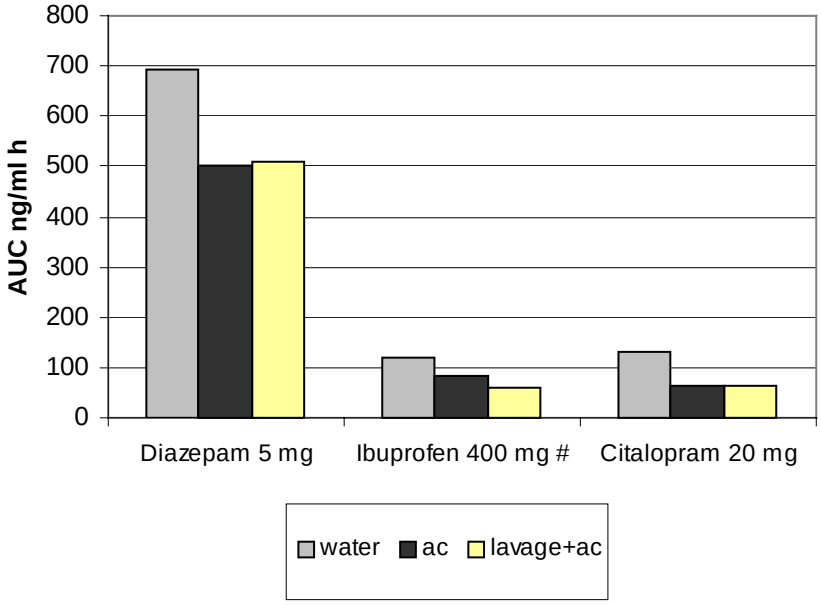


**Figure 8**: Mean AUC(0-10) of diazepam, ibuprofen, and citalopram. Treatments were activated charcoal (ac) (25 g) alone or preceded by gastric lavage started 30 min after drug intake. # for ibuprofen, AUC is µg/ml h.

## 6.3. Activated charcoal alone and followed by whole-bowel irrigation

For sustained-release drugs, activated charcoal alone was compared with charcoal followed by whole-bowel irrigation. Some differences between the treatments were dependent on the drug studied.

Carbamazepine: Both activated charcoal alone and charcoal followed by whole-bowel irrigation significantly reduced the absorption of carbamazepine compared with control values. Reduction in the AUC(0-24) and $C_{max}$ was significantly ($P < 0.01$ and $P < 0.05$, respectively) smaller after combination treatment than after activated charcoal alone (Figure 9).

Theophylline: Both treatments reduced the AUC(0-24), $C_{max}$, and $C_{\Delta}$ of theophylline significantly ($P<0.001$), but differences between the treatments were not statistically significant (Figure 9).

Verapamil: Both treatments reduced significantly ($P<0.001$) the AUC(0-24) ($P<0.001$) as well as the $C_{max}$ ($P<0.01$) of verapamil (Figure 9). The combination treatment reduced $C_{\Delta}$ by 79% ($P<0.001$) and activated charcoal by 73% ($P<0.01$), but the difference between the treatments was not significant.

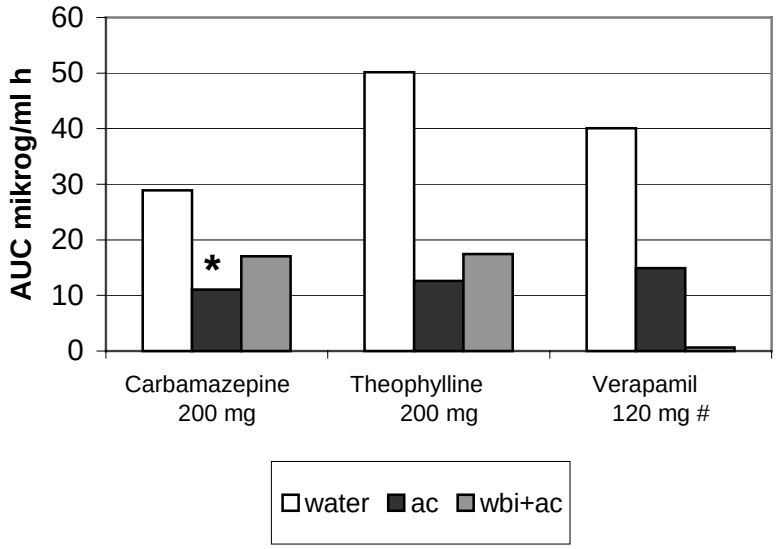


**Figure 9**: Mean AUC(0-24) of sustained-release formulations of carbamazepine, theophylline, and verapamil after activated charcoal (ac) (25 g) alone or charcoal followed by whole-bowel irrigation (wbi). Treatments were started 1 h after drug intake. # for verapamil, AUC is multiplied by 100. * Significantly ($P<0.01$) different from wbi+ac.

# DISCUSSION

## 1. METHODOLOGICAL CONSIDERATIONS

Study populations in epidemiological studies worldwide have varied from millions (McCaig and Burt 1999) to less than one hundred (Hawton et al 1996, Tay et al 1998) depending on the focus of the study. In our two epidemiological studies (I-II), the number of patients was relatively small but represented well the Finnish population, since the studies were conducted in Meilahti Hospital (part of the University Hospital, Helsinki), and at that time practically all the adult poisoned patients of the area (about one million population) were treated there.

Properly conducted reliable studies with poisoned patients are difficult to perform. The largest clinical studies have involved over 800 patients (Merigian et al 1990, Pond et al 1995), but still these studies were unable to confirm the benefit or disadvantage of gastric lavage, especially for severe intoxication, which had been their objective (AACT, EAPCCT 1997a). Many poisoning patients who present to hospital are, however, otherwise healthy and thus resemble healthy subjects, which justifies the volunteer studies. The number of volunteers in Studies III to VI was considered to be sufficient to discover clinically significant differences between treatments, but, on the other hand, useless exposure of healthy volunteers to drugs was avoided. By using healthy volunteers, we were able to standardise many variables like drug dose, concomitant medications, delay in presentation, and stomach contents.

However, extrapolation of the results from healthy volunteers to overdosed patients should be done with some caution. The dose of activated charcoal in our studies was 25 g, and the drug doses tested were, of necessity, therapeutic, which resulted in a relatively high charcoal:drug ratio. It varied from 62.5:1 for ibuprofen to >1000:1 for diazepam, citalopram, and temazepam. However, even at a ratio of 10:1, 90 to 100% of most drugs are adsorbed onto charcoal in vitro (Neuvonen and Olkkola 1988), suggesting that the adsorption capacity of the normal single dose (50 g) of activated charcoal would not be

saturated even at a considerably higher dose of drugs than ingested in the present studies.

In the present studies, the delay from drug ingestion to treatments varied from 5 to 60 min, less than in usual overdose cases. This difference is, however, not so obvious, since in our studies each volunteer took drugs on an empty stomach, and the absorption of drugs started immediately, whereas in overdose cases absorption can be markedly delayed due to the ingested poison, to the contents of the stomach, and to other concomitant medications.

The drugs were chosen for our study according to certain criteria. They are all commonly involved in overdose cases, the doses used were safe for the volunteers, and their plasma concentrations should be measurable. The drugs should also not have important interactions between them caused by cytochrome P450 enzymes. Some study drugs, however, were metabolised by enzymes which exhibit a clear polymorphism: Ibuprofen (2C9), citalopram, diazepam, and moclobemide (2C19). In order to avoid the large interindividual differences due to this polymorphism, we used a cross-over design in all volunteer studies. Furthermore, the effect of activated charcoal on the absorption of citalopram, diazepam, ibuprofen, moclobemide, and temazepam had never before been studied.

Gastric lavage was performed while volunteers were sitting, although the international Position Statement for gastric lavage advises that the patient lie on his left side. A seated position was chosen because in Finland gastric lavage is usually performed in this way on conscious patients, and the two nurses assigned to this task were very experienced clinically in performing it thus. Whole-bowel irrigation, in contrast, was performed other than is usual in a clinical situation. We gave the irrigation solution to the volunteers orally, using no naso-gastric tubes as had all other studies. This route was chosen to help us study whether the required amount of solution could be drunk and whether invasive procedures could be avoided.

## 2. EPIDEMIOLOGICAL ASPECTS OF ACUTE POISONINGS

Our two epidemiological studies concentrated on adult poisonings, and no data were collected on childhood poisonings. Childhood poisoning is usually accidental, with plants, berries, and household products more often involved. In adults, self-poisoning is usually deliberate; in our study only 2.7% of cases were considered accidental. The common characteristic is that mortality is very low in acute poisonings treated in hospitals, in adults having been under 1% in most studies (Linné 1974, Jacobsen et al 1984, McGrath 1989). Most adult poisonings in Finland are caused by drugs, though alcohol is also often involved (in 67%) (Study I). Alcohol is also the most common non-drug agent; in our study it was the sole poison in 24% and 11% of cases in men and women, respectively. Other non-drug products like corrosives, solvents, and petroleum products had already shown a tendency toward decreased use in the 1980's (Lamminpää et al 1993), and there were only three such poisonings in our study. Another non-drug group not seen in our study was mushrooms. This was clearly due to the season, since poisonings caused by mushrooms are usually seen only in autumn.

The only notable exception in the non-drug group was illicit drugs like heroin or amphetamine. These were not even mentioned during the years 1978 to 1984 (Lamminpää 1991), but now they were causing 6.2% of all poisonings treated in hospital. This tendency seems to be on the increase, since, especially for younger men, illicit drugs are more popular poison-causing agents than is alcohol alone. It must be remembered that the great majority of minor poisonings resolve themselves outside hospitals, and we do not know whether in some regions illicit drugs have already displaced alcohol.

The illicit drugs are more commonly used by young people, and as our study indicated especially by young men. No other agent was so markedly connected with age. We also found other agents that showed significant differences between genders. Women took significantly more antidepressants than men, whereas men more commonly used alcohol alone. Alcohol combined with other agents was taken by both men and women.

Because most of the poisonings were suicide attempts or demonstrations, most of the drugs used were therefore those that were easily at hand. The most common drugs involved were anxiolytics (benzodiazepines), neuroleptics, antidepressants and zopiclone or zolpidem; the results showed which drugs had been prescribed to the patients. We divided the poisoning-causing drugs according to Pharmaca Fennica (1997), so sleeping pills like temazepam are included in anxiolytics, and zopiclone and zolpidem are in a class by themselves. During the 1980's, as now, psychotropic drugs, sleeping pills, and sedatives were the most common drugs in poisonings (Lamminpää 1993). At that time, however, cardiovascular drugs were in second position, and recently there have been just a few cases with these drugs. There are some explanations for this fact. The prescriptions for digoxin, which is rather toxic, have decreased, and except for calcium-channel blockers the cardiovascular drugs most used are rather nontoxic. Another significant difference is in the use of antibiotics. Poisonings due to these had already decreased between 1978 and 1984, and 1987 and 1988, and now played no role at all. These changes also reflect the changes in their use. The course of antibiotics is now shorter, and thus the number of the pills is lower. The influence of prescriptions on poisonings has been noticed also in the UK, where paracetamol overdoses decreased significantly after limitations were put on paracetamol availability (Turvill et al 2000). Prevention of poisonings is not, however, as the examples above would imply, the same as prohibiting the use of some drugs. On the contrary, Sweden experienced a huge increase in antidepressant use, but at the same time, the suicide rate decreased significantly, reflecting a real need for them (Isacsson et al 1997). In Norway, the Health Authorities recommended more restrictive attitudes when prescribing psychoactive drugs, leading to a decrease in such prescriptions. However, the total number of all overdose admissions remained unaltered, and patients used more drugs from non-medical sources (Ekeberg et al 1987).

A reduction in admissions for self-poisoning might be achieved by increasing psychiatric as well as social interventions directed to repeat poisonings. In our study, 4% of patients were admitted more than once. This number might have been larger if the study had lasted longer, since in another study the mean interval to repetition was three months, and 9% of patients were admitted more than once (McEvedy 1997). Similarly,

Hawton and Fagg (1992) reported nearly one-third of their patients with a history of earlier attempts.

Our second study (II) showed that the medical history obtained on admission is not always in accordance with toxicological analyses. In only 27% of the cases were the drugs correctly identified by the history, though in most cases the discrepancies between history and laboratory tests were only minor. However, 20% of cases showed clinically important differences. Other studies have also confirmed the discrepancy between history and laboratory tests. Of 140 overdosed patients in England, an exact correspondence occurred in only 45% of cases (Wright 1980). It was more common for patients to exaggerate the poisoning than to underestimate it, just as in our study. On the other hand, Rygnestad et al (1990), who compared histories and laboratory findings in 1978 and 1987 in Norway, found that the main drug taken was correctly identified on admission by 86% (n=228, 1978) and 96% (n=383, 1987). The discrepancies concerned mostly secondary drugs, which, however, may also be dangerous; some drugs can cause serious poisoning even in small amounts or can produce interaction toxicity. Toxicological analysis was found to be rather useless by Mahoney et al (1990) who evaluated 176 cases of drug overdose: They found that treatment was usually based on clinical parameters rather than on laboratory results.

In order to obtain as reliable results as possible, in our first study (I) we combined the results of histories and laboratory tests. All dangerous drugs were identified precisely, since the patients and possible complications were followed as long as they stayed in hospital; this follow-up showed that no life-threatening drug had been unidentified at admission.

In our study (I), 9% of patients received an antidote, flumazenil in most cases, calcium gluconate in three cases, and naloxone in one case. National characteristics are evident here. In the UK, N-acetylcysteine has been the most popular antidote (Thomas et al 1996b), though the number of patients receiving an antidote was very similar (6%) to figures in our study. In contrast, in Norway 21% of patients received an antidote, reflecting the fact that all benzodiazepine poisonings were treated with flumazenil

(Jacobsen et al 1984). The use of gastric lavage has decreased during the last few decades. In the 1980's in Norway all patients who had ingested some other poison than corrosives or petroleum products received gastric lavage, irrespective of the time-interval (Jacobsen et al 1984), while only 55% of British patients (Thomas et al 1996b) and 57% of Turkish patients (Özköse and Ayoğlu 1999) were treated with lavage in the 1990's. In our study, gastric lavage was performed for half the cases, while most patients received at least one 50 g dose of activated charcoal; 15% of patients received whole-bowel irrigation.

## 3. THE EFFECT OF ACTIVATED CHARCOAL AND GASTRIC LAVAGE

The effect of gastric lavage and activated charcoal was studied in three randomised, controlled, volunteer studies (Studies III-V). One of them compared activated charcoal with gastric lavage followed by charcoal (III), and two others compared charcoal alone to lavage alone (IV-V). The effect of charcoal was also studied 1 h after the ingestion of sustained-release drugs (VI), and those results are related to those, with whole-bowel irrigation. Time-intervals between ingestion of drugs and gastric lavage were either 5 min or 30 min, the latter time to simulate conditions in patients presenting soon after an overdose. Although poisoned patients often present several hours after ingestion of the toxic agent, some patients do present without delay (Thomas et al 1996a). Five minutes, which was used in our studies, revealed the efficacy of both treatments immediately after ingestion.

Temazepam, verapamil, and moclobemide were used to compare the effect of gastric lavage alone and activated charcoal alone 5 min and 30 min after their ingestion. When gastric decontamination procedures were applied 5 min after ingestion, activated charcoal was superior to gastric lavage in preventing the absorption of all drugs. Reductions in the AUC(0-24) of temazepam, verapamil, and moclobemide caused by activated charcoal (95.2%, 92.8%, and 99.7%, respectively) were significantly greater than the reductions after gastric lavage (25.6%, 4.0%, and 34.6%). The poor efficacy of gastric lavage is thought to be due to the incomplete disintegration of the study drugs. In

vitro in 0.1N HCl, the disintegration time of temazepam capsules was 9 to 10 min and that of verapamil and moclobemide tablets 20 to 25 min, indicating that these drugs had not disintegrated before lavage was started. Since the length of an intact tablet or capsule was 9 to 16 mm, they were not easily washed out of the stomach through an orogastric tube (inner diameter 8 mm).

Thirty minutes after their ingestion, the mean AUC(0-24) of moclobemide, temazepam, and verapamil was reduced by 33 to 55% by activated charcoal and by 18 to 44% by gastric lavage. Reductions in absorption of verapamil and moclobemide by activated charcoal and gastric lavage were similar. However, absorption of temazepam was reduced significantly more by charcoal. This was the first study in which gastric lavage followed drug ingestion by 30 min, and it seems that at that interval both treatments may show some clinical benefit. The small differences between study drugs were probably due to the considerable intersubject variation, for instance, 90% of the absorption of verapamil was prevented by charcoal in two subjects; when all nine subjects were combined, values were no longer significantly different from control values.

Charcoal alone, or gastric lavage followed by activated charcoal, were equally effective in preventing the further absorption of diazepam and ibuprofen 30 min after ingestion. Both treatments reduced the AUC(0-10) of citalopram by 51% and that of diazepam by 27%; the AUC(0-10) of ibuprofen fell by 30% and by 49% after charcoal alone and after charcoal preceded by lavage. Every reduction was significantly different from the control value. Furthermore, the greatly reduced or even negative $C_{\Delta}$ of diazepam and ibuprofen indicated the good efficacy of both gastric decontamination procedures in preventing further absorption of these drugs from 0.5 h onward. Citalopram, on the other hand, was slowly absorbed, and its plasma concentrations continued to increase for several hours after the interventions. The increase was, however, smaller in the treatment phases than in the control phase, and the $C_{\Delta}$ of citalopram was also significantly different from the control value.

Other volunteer trials have also shown the good efficacy of charcoal (25 g or 50 g) administered immediately after drug ingestion (AACT, EAPCCT 1997b). The mean

reduction was 93% but it varied from 64% for valproate (Neuvonen et al 1983a) to 100% for amitriptyline (Kärkkäinen and Neuvonen 1986), carbamazepine, and phenobarbital (Neuvonen and Elonen 1980), chlorpropamide (Neuvonen and Kärkkäinen 1983), cimetidine and pindolol (Neuvonen and Olkkola 1984a), diphenhydramine(Guay et al 1984), quinidine (Neuvonen et al 1984), and trimetoprim (Neuvonen and Olkkola 1984b). Reduction is dependent on the formulation of the drug, as shown by Laine et al (1997c). In that study, immediately after drug ingestion, the reduction in absorption of ordinary verapamil was 99% but that of slow-release verapamil only 86%. Studies in which activated charcoal is administered 30 min after drug ingestion are not so many, and the efficacy of charcoal has varied from 31% to 75%, on average 54% (Levy and Houston 1976, Dawling et al 1978, Sintek et al 1979, Sketris et al 1982, Neuvonen et al 1983b, Ekins et al 1987). In our studies, charcoal given after a 30-min lag-time reduced the absorption of various drugs by 27% to 55%, well in line with previous reports.

That the antidotal efficacy of activated charcoal is better the shorter the lag-time in its administration is a general finding which our results confirm. Activated charcoal is recommended for use up to 1 h after ingestion of a drug overdose, but this recommendation is based on ordinary formulations (AACT, EAPCCT, 1997b). Only a couple of studies concern the efficacy of charcoal after intake of sustained-release drugs (Neuvonen et al 1983b, Lim et al 1986, Minton et al 1995, Laine et al 1997c), and show that charcoal can still be highly effective 1 h or even more after ingestion of sustained-release tablets, as in our study as well.

It must be remembered, however, that though charcoal is very effective in preventing the absorption of many drugs and is rather convenient to use, there are also many substances which are not adsorbed by charcoal. In intoxication with lithium, for instance, other treatments must be used.

The efficacy of gastric lavage seems to vary more than does that of charcoal, and its correlation with time-intervals is not as clear as in the case of charcoal. The recovery of liquid thiamine has been as high as 90% by gastric lavage 5 minutes after its ingestion

(Auerbach et al 1986). Tandberg et al (1986) performed gastric lavage 10 minutes after 18 healthy volunteers each took 25 tablets of cyanocobalamin; the mean recovery of cyanocobalamin was only 45% (range 19-68%). When 17 volunteers ingested 30 gelatin capsules containing a nonabsorbable radionuclide marker, and gastric lavage was performed 9 to 42 min (mean 19 min) later, the mean tracer recovery was 30% (Young and Bivins 1993). In no volunteer studies has gastric lavage been performed 30 min after drug ingestion; in those performed 1 h after ingestion, gastric lavage results did not differ from control results (Tenenbein et al 1987a, Danel et al 1988, Minton et al 1995). Only Christophersen et al (1999) has compared charcoal alone to lavage followed by charcoal. The time interval was 1 h in that study, which showed no significant difference between treatments. In our studies, gastric lavage alone reduced the absorption of drugs by 4 to 32% and by 18 to 43%, at a respective 5 and 30 min after ingestion. When lavage was followed by charcoal, reductions were 27 to 51% at 30 min after ingestion.

The obvious difference between our study (IV) and that of Auerbach et al (1986) is probably the different formulations of the drugs. They used liquid thiamine, and our drugs were all capsules or tablets. The main reason that our gastric lavage was surprisingly ineffective was probably the aforementioned incomplete disintegration of the drugs.

Disintegration times of different formulations vary and depend on such factors as stomach contents and number of tablets ingested, making the effect of gastric lavage rather unpredictable. The effect of activated charcoal also depends on many factors like dose, and the time-interval after ingestion of poison. However, factors affecting the antidotal capacity of charcoal are well studied, and the position of charcoal in acute intoxication is more precise than that of gastric lavage.

Although these studies were performed in healthy volunteers, the findings may, with some caution, be applied to the management of overdose patients. To summarize, when gastric decontamination methods are performed immediately after drug ingestion, activated charcoal is superior to gastric lavage. When they are performed 30 min after ingestion, activated charcoal maintains its efficacy moderately, with gastric lavage

apparently becoming less effective. These results are supported by a large clinical trial showing no difference between patients receiving activated charcoal only and receiving charcoal + gastric emptying (Pond et al 1995). The efficacy, the convenience, and the superior safety of activated charcoal for overdose patient have been noticed by clinicians. When treatment methods for acute poisonings over a 10-year period (1980-1990) were assessed, use of gastric emptying methods had fallen from 75% of cases to 13% (MacNamara et al 1996). Based also on our studies, activated charcoal can be recommended for use as soon as possible, with no gastric decontamination methods added, if the poisoning-causing agent is adsorbable by charcoal.

## 4. THE EFFECT OF WHOLE-BOWEL IRRIGATION

Whole-bowel irrigation is used in the management of sustained-release drug overdose and is usually combined with administration of activated charcoal. We therefore compared the efficacy of charcoal alone to that of irrigation after charcoal 1 h following ingestion of sustained-release carbamazepine, theophylline, and verapamil. The reduction in absorption of the study drugs by charcoal alone was 62% to 75%, and charcoal followed by PEG solution reduced drug absorption by 41% to 85%. In the case of theophylline and verapamil, both treatments' results differed significantly from control values, and no significant difference existed between treatments. On the other hand, though both treatments prevented significantly the absorption of carbamazepine, charcoal alone was significantly better; and in combination treatment, PEG solution actually reduced the effect of charcoal.

Studies of whole-bowel irrigation are very few, and only one compares use of activated charcoal to charcoal followed by whole-bowel irrigation (Rosenberg et al 1988). For this study, with only three volunteers, charcoal alone seemed the most effective treatment. Three other studies have studied whole-bowel irrigation with controls, finding that for ampicillin, delayed-release aspirin, and sustained-release lithium, whole-bowel irrigation significantly reduced their bioavailability: by 67%, by 73%, and by 67% (Tenenbein et al 1987b, Kirschenbaum et al 1989, Smith et al 1991).

There was one essential difference between these studies of whole-bowel irrigation and our study. In each of them, PEG solution was given by naso-gastric tube at a rate of 2 l/h, for a total volume of almost 10 l. This volume and rate are routinely recommended, but there seems to exist no explanation, and no clinical studies concern the use of whole-bowel irrigation. We studied whether the amount of PEG solution needed could be drunk, thus avoiding the invasive use of a naso-gastric tube. The mean irrigation time in our study was 1 hour 54 minutes, and the mean total volume of PEG solution consumed 1.6 l, making the rate much slower and amount smaller than in the earlier reports. Because one common complication of whole-bowel irrigation is nausea and even vomiting caused by the solution, a slower infusion (or drinking) rate could ease the situation.

As studies concerning the use of activated charcoal or whole-bowel irrigation in the management of sustained-release drug overdoses are so scarce, conclusions as to clinical situations should be drawn carefully. Activated charcoal alone was still effective in our study 1 h after ingestion of carbamazepine, theophylline, and verapamil; similar results appear in other studies (Neuvonen et al 1983b, Lim et al 1986, Minton et al 1995, Laine et al 1997c). Charcoal reduced the AUC of a simulated sustained-release theophylline overdose 1 h after ingestion by 83% (Minton et al 1995) (vs. 75% in our study). Laine et al (1997c) found that charcoal reduced the absorption of sustained-release verapamil by about 35% (significantly) even 2 h and 4 h after drug ingestion. Therefore, the tentative limit of 1 h should be discarded for poisonings with sustained-release formulations, and if the drugs ingested have a high affinity to charcoal, charcoal should still be administered after 1 h.

The issues surrounding whole-bowel irrigation become still more complicated. One case report of three patients demonstrates some efficacy for PEG solution together with charcoal in slow-release verapamil poisonings (Buckley et al 1993). However, in our study the absorption of slow-release verapamil as well as of theophylline was equally well prevented by charcoal alone and by the combination treatment. This is, however, not the case with all drugs. The present study showed whole-bowel irrigation to reduce

the efficacy of activated charcoal in preventing absorption of carbamazepine. There is also one in vitro study in which PEG solution significantly reduced the adsorption of theophylline onto activated charcoal (Hoffman et al 1991), so it seems there may be some competition between a drug and PEG solution for available charcoal-binding sites.

The pharmacokinetics of the drugs, their adsorbability onto charcoal, and the properties of sustained-release formulations can thus be decisive in determining which treatment is preferable. Whole-bowel irrigation definitely has its role in poisonings by slow-release formulations of some drugs, as Buckley et al (1993) showed, but because it may even reduce the antidotal effect of activated charcoal, its use should be viewed critically if the overdose drug is effectively adsorbed by charcoal.

## CONCLUSIONS

On the basis of these studies, the following conclusions can be drawn:

1. Acute poisonings are usually not caused by one main agent alone; several drugs or drugs and alcohol are often involved. Moreover, patients do not give a reliable medical history concerning the agents taken.

2. Discrepancies between the history and laboratory findings are usually not clinically significant.

3. Citalopram, diazepam, ibuprofen, moclobemide, and temazepam are all adsorbable by activated charcoal.

4. Activated charcoal effectively prevented the absorption of all the study drugs both 5 min and 30 min after their ingestion.

5. Gastric lavage had no significant effect on absorption of the study drugs when performed 5 min after their ingestion, and it was less effective than was charcoal when lavage was done and charcoal was given 30 min after ingestion.

6. Charcoal can be given alone or preceded by gastric lavage. Lavage does not, however, add any additional benefit to charcoal when the drugs are well adsorbable to charcoal.

7. Activated charcoal, given 1 h after drug ingestion, is an effective gastric decontamination method for sustained-release formulations. The efficacy of whole-bowel irrigation is, however more unpredictable and differs with different drugs. Furthermore, it may even reduce the efficacy of charcoal.

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