OLLI IMPIVAARA

Utilization of Cardiac Glycosides in Finland

Turku 1986
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Sydänglykosidien käyttö Suomessa

Turku 1986


Tämän tutkimuksen tavoite oli arvioida kuinka laajaa ja vaihtelevaa ja kuinka tarkoituksenmukaisista digitalisvaluimisteiden käyttö Suomessa on. Tavoitteena oli lisäksi selvittää millä tavoin digitalishoitoa maassamme toteutetaan ja miten sitä valvotaan.

Aineisto ja menetelmät

Tämä tutkimus on osa Kansaneläkelaitoksen laajaa Mini-Suomi-terveysstudiumista, jota toteutetaan Kansaneläkelaitoksen kuntoutustutkimuskeskuksen ja Sosialiturvan tutkimuslaitoksen yhteistyönä. Mini-Suomi-tutkimuksen yleisenä tavoitteena on tuottaa tietoa ja kehittää menetelmiä, joita tarvitaan sairauskseen ja työ- ja toimintakyvyyn heikkenemisen ehkäisemisessa, hoidon ja kuntoutuksen kehittämisessä sekä terveydenhuollon toimintojen suunnittelussa ja arvioinnissa.

Tutkimus kohdistui 30 vuotta täyttänyttä väestöä edustaneeseen 8000 henkilön otokseen. Se käsitti terveyshaastattelun ja tervey斯塔kustuksen. Terveyshaastattelun toteuttavat paikalliset terveydenhoitajat tutkittavan kotona. Tervey斯塔kustuksen teki Kuntoutustutkimuskeskuksen kenttäyksikkö, Autoklinikka tutkittavan kotipaikkakunnalla. Aineisto kerättiin vuosina 1977-80. Terveyshaastatteluun osallistui 7703 henkilöä (96,3 % otoksesta) ja ter-
veystarkastukseen 7217 henkilöä (90,2 % otoksesta). Koska otos oli edustava ja tutkimuksesta poisjääneitä oli vähän, tulokset voidaan yleistää koskemaan koko perusjoukkoa, s. o. Suomen 30 vuotta täytätynä väestöä.


Tulokset

Digitalisvalmisteiden käytön todettiin olevan vielä laajempaa kuin lääkkeiden myynttilastojen perusteella aiemmin on viitoit arvioida. Digitalisken käyttöä osoittava merkitsevä seerumin digitalispitoisuus todettiin n. 9 %:lla miehistä ja n. 10 %:lla naisista. Näiden esiintyvyytslukujen perusteella arvioitiin digitalishoidossa olevien suomalaisten vähimmäismääriksi 248000 (±21000). Haastattelujen ja kyselytietojen mukaan digitalisvalmisteita käytti n. 10 % miehistä ja n. 11 % naisista. Tällä perusteella arvioitiin digitalisken käyttäjä olevan Suomessa kaikkiaan 311000 (±22000). Digitalisvalmisteiden käytön todettiin yleistynyt voimakkaasti iän mukana. Noin 65 % käyttäjistä oli 65-vuotiaita tai sitä vanhempia. Käytöstä 90 % tapahtui avohoidossa.


Keskimäärin joka kolmannen digitalishoidossa olevan potilaan seerumin digitalispitoisuus alitetti yleisesti suositeltun hoitoalueen alarakkaan. Tällainen kyseenalaiseen, huonosti kontrolloituun tai epätarkoituksenmukaiseen digitalishoitoon viittaava löydös oli Etelä-Suomessa ja Itä-Suomessa selvästi yleisempi kuin muualla maassa.
Yli 90 % kaikista digitalisvalmisteiden käyttäjistä käytti digoksiinia, tavallisimmin yhtenä päiväannoksena. Vain harvoilla digoksiinin käyttäjillä vuorokausiannos oli suurempi kuin 0,25 mg. Seerumin keskimääräinen digoksiinipitoisuus oli sekä miehillä että naisilla noin 1 ng/ml.

Suurin osa digitalisvalmisteiden käyttäjistä käytti samanaikaisesti ainakin yhtä muuta reseptilääkettä. Digitalista käyttävillä miehillä oli käytössä keskimäärin 4,2 reseptilääkettä. Naisilla keskimääräinen reseptilääkkeiden lukumäärä oli vastaavasti 4,6.

Noin 85 % kaikista digitaliksen käyttäjistä oli "oman" lääkärin hoidossa. Melkein kaikki digitalista käyttäneet potilaat ilmoittivat käyneensä lääkärissä tutkimusta edeltäneen vuoden aikana ainakin kerran. Kuitenkin vain noin puolet potilaista oli selvästi sopinut lääkärin kanssa seuraavan käynnin ajankohtasta. Potilaista noin 20 %:lla ei ollut mitään tietoa seuraavasta käynnistä ja 25 % ilmoitti menevänä seuraavan kerran lääkäriin "vain tarvittaessa" tai ajankohtana, jota eivät osanneet tarkemmin määrittellä.

Johtopäätökset

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Abstract


The study is part of the Mini-Finland Health Survey of the Social Insurance Institution, the general aim of which is to shed light on the state of health of the population, on the consequences of disease, on the total need for health services and on the adequacy of the services provided. A sample representative of the Finnish population aged 30 or over is being studied. The aim of the present study was to estimate the extent, variation and adequacy of the use of cardiac glycosides (digitalis preparations) in Finland. The methods comprised questionnaires, interviews, measurement of serum digitalis content, chest X-ray and ECG. The use of cardiac glycosides was found to be exceptionally widespread. About 10 % of men and 11 % of women were receiving these drugs. The extent of use varied remarkably between regions within the country. Much of the use was considered inappropriate or questionable. These findings suggest that the use of cardiac glycosides needs thorough reappraisal in this country.

Key words: digitalis glycosides; drug utilization; interviews; questionnaires; radioimmunoassay; sampling studies

Tiivistelmä


Avainsanat: digitalisglykosidit; lääkkeiden käyttö; haastattelut; kyselyt; digitalismääritykset; otantatutkimukset
FOREWORD

This study is part of the Mini-Finland Health Survey, which is being jointly carried out by the two research units of the Social Insurance Institution, the Rehabilitation Research Centre, Turku, and the Research Institute for Social Security, Helsinki. The ultimate aim of the Mini-Finland Health Survey is to provide information and develop methods which can be used to prevent disease and disability, to improve treatment and rehabilitation and to plan and evaluate health services. The present study was undertaken to evaluate the use of cardiac glycosides in Finland.

I wish to express my profound gratitude to Mr. Jaakko Pajula, Director-General, and other members of the Board of the Social Insurance Institution for making this research possible.

I extend my deepest and most sincere thanks to Professor Veikko Kallio, M.D., Director of the Rehabilitation Research Centre, and to Professor Esko Iisalo, M.D., Head of the Department of Clinical Pharmacology, University of Turku, for their patient support and advice throughout the study. Professor Iisalo also kindly arranged for the serum digitalis concentrations to be measured under his supervision at the Department of Pharmacology. I am greatly indebted to him for all his help.

I am very grateful to Dr. Jouni Maatela, Chief Physician of the Mobile Clinic Unit of the Social Insurance Institution, for the pleasant working atmosphere, experienced advice and many inspiring discussions. I express my deep gratitude to Docent Arpo Aromaa, M.D., Director of the Medical Research Group of the Research Institute for Social Security. His vast experience and knowledge of epidemiology, his constructive criticism and encouraging propositions have been of indispensable help to me. My sincere thanks are also due to Docent Antti Reunanen, M.D., who made valuable contributions to the study.

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The author
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1. LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following original papers, which are referred to as I-IV in the text:


IV Olli Impivaara, Jouni Maatela, Arpo Aromaa, and Antti Reunanen: Practice and control of digitalis therapy in Finland. Submitted for publication.
2. INTRODUCTION

Adequate drug therapy is an essential part of good medical care. It is the main goal of drug utilization studies to assess whether drugs are used adequately or not.

Cardiac glycosides are among the most commonly-prescribed drugs. More than 300 natural or semisynthetic cardiac glycosides are known but only a few of these are in clinical use (Smith and Braunwald 1980). In Finland three digitalis glycoside derivateiv (digoxin, digitoxin and lanatoside C) and one scilla glycoside (proscillaridin A) are available for oral use (Nordic Statistics on Medicines 1982b). In the present report these glycosides will simply be referred to as "digitalis" or "digitalis glycosides". The main emphasis will be put on digoxin, the predominant glycoside in Finland.

Digitalis has two clinically significant actions. Firstly, it has a positive inotropic action on the myocardium. This action makes it useful in heart failure. Secondly, digitalis slows atrioventricular conduction by a direct effect on the A-V node and indirectly by increasing vagal tone. These actions constitute the basis for the use of digitalis in supraventricular tachyarrhythmias (Braunwald 1980, Hoffman and Bigger 1980, Fishman 1982).

Because of its potential toxicity and exceptionally narrow margin of safety digitalis should be used with great caution and only if the indications are well defined. However, although digitalis has been in clinical use for more than 200 years, the indications are still not completely established. Digitalis is clearly indicated in atrial fibrillation with fast ventricular response and it is often useful in acute heart failure. In contrast, there is substantial controversy about the usefulness of digitalis in the long-term management of heart failure, especially in patients with sinus rhythm (Editorial 1978, 1979, 1982, Guz and McHaffie 1978, Taggart and McDevitt 1980, Counihan 1982, Hamer 1982, Storstein 1982, Fleg and Lakatta 1984, Mulrow et al. 1984, Chamberlain 1985, Wilkins et al. 1985). Many patients may therefore be taking digitalis unnecessarily. On the other hand, there may be patients who have clinical indications for digitalis but who are not receiving it (Storstein 1982).

The dosage of digitalis is problematic (Aronson and Grahame-Smith 1976, Dobbs et al. 1977, Liverpool Therapeutics Group 1978, Lee and Smith 1983) and patients notoriously comply poorly with this therapy (Johnston et al. 1978, Johnston and McDevitt 1978). Many patients may therefore be taking digitalis inappropriately.
Comparative statistics have shown remarkable qualitative and quantitative differences in the sales of digitalis glycosides between several European countries (Nordic Statistics on Medicines 1979, 1982a, Friebel 1982). According to these statistics digitalis consumption appears to be exceptionally widespread in Finland. Hence, it seemed pertinent to study in detail the utilization of digitalis glycosides in this country. The Social Insurance Institution's Mini-Finland Health Survey, which was based on a large representative adult population sample, offered an excellent opportunity for such a study.
3. REVIEW OF THE LITERATURE

3.1. Drug utilization studies

3.1.1. Concept and purposes of drug utilization studies

Drug utilization has been defined by a WHO expert committee as "the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (WHO 1977). However, it should be noted that marketing, distribution and prescription are merely factors that modify the actual use of drugs, which is the central object of interest in drug utilization research.

The use of drugs undoubtedly is an essential part of modern health care. There has, however, been concern that much of the drug use may be unnecessary or inappropriate and even harmful (Lunde et al. 1979, Wade 1979, Gross 1981, Crooks 1984). These views have been supported by recent studies, which have shown remarkable qualitative and quantitative differences in drug prescribing between countries and even between regions within countries (Lawson and Jick 1976, Bergman 1979, Grimsson et al. 1979, Nordic Statistics on Medicines 1979, 1982a, Friebel 1982, Baksaas 1984).

Questionable drug therapy exposes patients to unnecessary risks of drug toxicity and needlessly increases the cost of health care. On the other hand, underprescribing and lack of drug compliance may be equally harmful. For these reasons more should be known about the benefits and side effects of the drugs that are prescribed and about the doctors who prescribe them (Boethius 1977, Lunde 1977, Slone et al. 1979, Wade 1979, Gross 1984).

Drug utilization studies aim to evaluate the efficacy and safety of drug therapy and to define areas where further research should be directed. The results can be used to identify overuse, underuse or misuse of single drugs or groups of drugs and to modify drug prescribing accordingly (Boethius 1977, Lunde 1977, WHO 1977, Bergman 1978, Lunde et al. 1979). Such "therapeutic audit" may assist both in increasing the quality and reducing the cost of health services (Ogilvie and Ruedy 1972, Boethius 1977, Crooks 1979, 1984, Eisenberg and Williams 1981, Avorn and Soumerai 1983, Tognoni 1983).
3.1.2. Methods for assessing drug utilization

3.1.2.1. Levels of drug utilization studies

Drug utilization can be studied at various levels (Lunde et al. 1979):

1. The studies may concentrate on all drugs, groups of drugs (according to anatomical, chemical or therapeutic classification), or single drugs.

2. Information on drug utilization may be collected from various areas or sources: whole countries, regions within countries, pharmacies, health insurance services, hospitals, physicians or patients.

3. The studies may be based on wholesale statistics, prescriptions, patients' drug intake or individual pharmacokinetic or pharmacodynamic indices such as plasma levels or measurable pharmacologic effects.

4. The measurements may be based on cost or quantity (for example as tablets or doses expressed as the weight of the active substance).

3.1.2.2. Classification of drugs and units of measurement

To classify drugs the so called Anatomical therapeutic chemical classification (ATC) has been recommended by the WHO Drug Utilization Research Group and by the Nordic Council on Medicines (Nordic Statistics on Medicines 1982b). In this classification each pharmaceutical speciality is given an ATC-code which is composed of five levels indicating the anatomical main group, the therapeutic main group, the therapeutic subgroup, the chemical/therapeutic subgroup and finally the subgroup of the chemical substance. For example, all digoxin preparations are given the code C 01 A A 05.

Using cost as a unit of measurement has several disadvantages. Due to price changes, the expenditure is not necessarily directly related to the volume of drug utilization in a given period of time and variable exchange rates may confuse international comparisons (Lunde et al. 1979). The units of quantity should therefore be preferred, especially if applied to single well defined products (WHO 1971, Lunde et al. 1979). The principle of defined daily dose (DDD) has been developed for quantitative measurements and comparisons of drug consumption statistics. This unit of measurement is recommended by both the WHO Drug Utilization Research Group and the
Nordic Council on Medicines (Lunde et al. 1979, Nordic Statistics on Medicines 1982b). The DDD is only a technical unit of measurement based on the recommended average daily maintenance dose for an adult. The real prescribed daily doses may therefore differ from DDD. Moreover, not all purchased drugs are likely to be actually used. Despite these discrepancies the DDD/1000 inhabitants/day can identify major differences in drug utilization between countries and regions (Lunde 1977, Lunde et al. 1979, Crooks 1984). If the drug is for continuous daily use, the DDD/day can give a general estimate of the number of patients using the drug (Nordic Statistics on Medicines 1982b).

3.1.2.3. Sources of information

Records of manufacturers and importers

Most manufacturers and importers collect information on production and import of drugs for their own commercial use. This information is not usually available for research purposes because the companies consider it confidential (Dukes 1979, Wade 1979). However, because drugs may be stored for indeterminate periods after they have been manufactured or imported, these records do not reliably reflect the drug consumption or even the sales of drugs within a given period of time (WHO 1971). For drug utilization studies this information would, therefore, be of limited value.

Records of drug distributors

The sales and distribution systems differ markedly between countries. In some countries, such as Sweden and Norway, drugs are traded by a single wholesale firm, which distributes all imported and domestic drugs to hospitals and pharmacies (Nordic Statistics on Medicines 1982a). In this system the wholesale statistics on all drugs, groups of drugs and single drugs can be expected to reflect the true drug consumption fairly reliably. In Finland drugs are dispensed to pharmacies by several independent wholesale firms, which also directly supply drugs for hospital use. Finnish hospitals may also purchase drugs direct from importers or domestic manufacturers (Nordic Statistics on Medicines 1982a). Since 1978 the annual statistical information on sales of medicines in Finland is based on total sales from wholesalers to pharmacies. The statistics do not include direct sales to hospitals. The volume of the direct sales to hospitals has been estimated at 15% of the total sales of medicines in Finland (Nordic Statistics on Medicines 1982a).
Not all medicines that have been purchased, are used, and the actual use can be spread over indeterminate periods of time (Nordic Statistics on Medicines 1982a). Different figures of sales of drugs between countries should therefore be interpreted with caution. Finding out the mean actual daily dose may help to interpret drug utilization figures based on the DDD (Bergman 1978). The sales statistics can raise questions about the reasons for apparent differences between countries and thus identify areas where further studies should be directed (Lunde 1977, Crooks 1984), but they can never replace studies made at the patient-physician level (Lunde 1977, Bergman 1978).

Physicians' records and prescriptions

Physicians' records can provide useful information on drug utilization because they link the prescribed drugs to individual patients: their age, sex, diseases, symptoms etc.

In Western European countries market research companies gather information on the prescribing habits of physicians. This information is collected for commercial purposes from a sample of physicians who are paid for delivering it (Wade 1979, Tognoni 1983). A disadvantage of this method is that the results are not generally available. Moreover, the representativeness of the samples of physicians and the accuracy of the reports can be questioned (WHO 1971).

Special prescription surveys in which samples of physicians are asked to write the indication for the drug therapy along with the age and sex of the patient on a self-copying duplicate prescription form may yield more accurate and representative information (Crooks 1979, 1983, Agenäs and Jacobsson 1980, Jacobsson and Kristoferson 1980).

The prescriptions may also be surveyed at the level of pharmacy. This method may give useful information about the drugs prescribed and actually dispensed (brand name, dose, amount), the patient (age, sex) and the prescribing physician (specialist, nonspecialist), but the indication for the medication will not be available (Westerholm 1976, Boethius and Wiman 1977, Kristoferson and Wessling 1977, Skegg et al. 1977). Drug utilization figures derived from prescription surveys have been shown to be in good agreement with the wholesale statistics (Boethius 1977).
Hospital records

Use of drugs by hospitalized patients or those attending outpatient clinics have been studied in many countries (Jick et al. 1970, Miller 1974, Lawson and Jick 1976, Westerholm 1976, Moir et al. 1979). These studies have been mainly aimed to detect side effects and interactions of commonly used drugs, to estimate the efficiency of these drugs and to characterize patients who are likely to present problems of drug toxicity or questionable efficacy.

Records of sickness insurance systems

The schemes according to which the cost of drugs to the patient are reimbursed are variable. In Finland the expenditure on partly or fully reimbursed drugs and the number of prescribed drugs can be obtained from the national sickness insurance statistics. Even though the statistics cover more than 90% of the prescriptions (Olli 1975) their value in drug utilization studies is limited because the figures are not available by single drugs or therapeutic groups of drugs.

Consumer surveys

Consumer surveys are the only way to obtain information on the extent to which drugs are actually consumed after they have been prescribed and dispensed (WHO 1971, Westerholm 1976). The surveys can also give valuable information about the drug consuming patients: their diseases, symptoms and socioeconomic status. One of the main advantages of consumer surveys is that if they are carried out in representative population samples, the results may be generalized to the total population. Such surveys, however, are rather expensive, laborious and difficult to perform (Lunde 1977, Baksaaas 1980).

Interview methods have been used to evaluate the need for and utilization of health services, including the consumption of drugs. In Finland three large scale health interviews have been carried out (Kalimo et al. 1982). In these studies drug utilization was reported only in terms of cost and number of prescriptions with no reference to single drugs or therapeutic groups of drugs.

Personal interviews have been considered more reliable than self-administered questionnaires, since the interviewer can check at least some of the data from the appropriate documents. To reduce errors the recall period must not be too long and it should be distinctly demarcated. Such interviews have been considered sufficiently valid (Purola et al. 1974).
Poor patient compliance is very common. On the average, about 50% of the patients receiving long-term medication seem to deviate from the instructions (Sackett and Snow 1979). Interviews and pill counts reveal some of the non-compliance (Gordis 1979, Norell 1984). Direct detection of the drug, its metabolite or a marker substance from plasma or urine, however, is the most objective method for assessing whether the patient has taken the drug or not (Westerholm 1976, Gordis 1979, Baksaas 1980). Drug determination from plasma is also valuable in controlling the adequacy of a drug therapy and evaluating suspected drug intoxication. A disadvantage of this method is that the measurements can be applied only to drugs that give steady state plasma levels. Moreover, the sampling itself may encounter difficulties (Haynes 1979).

3.2. Pharmacology of digitalis glycosides

3.2.1. Cardiovascular effects

3.2.1.1. Inotropic effect

The basic mechanism of the inotropic effect of digitalis is not completely understood (Hayward and Hamer 1979, Hoffman and Bigger 1980, Noble 1980, Brody 1981, Wilkerson 1981, Lüllmann et al. 1982, Godfraind 1984). The effect seems to be mediated through an action on the transmembrane ionic transport. Digitalis is thought to inhibit Na-K-ATPase activity. Inhibition of this enzyme results in a transient rise in the intracellular sodium concentration. This further increases intracellular calcium content available to activate myofibrillar contraction (Smith 1973, Hayward and Hamer 1979, Hoffman and Bigger 1980, Brody 1981). The inotropic effect has been demonstrated both in the normal and in the failing heart. The positive inotropic effect of digitalis increases progressively (up to its maximum) with increasing dose of the drug (Smith and Braunwald 1980).

3.2.1.2. Cardiac electrophysiologic effects

Inhibition of Na-K-ATPase increases the refractory period of the specialized conduction tissues of the heart and decreases their conduction velocity. These effects slow the ventricular response in atrial fibrillation and flutter (Braunwald 1980, Hoffman and Bigger 1980, Wilkerson 1981).

On the other hand, digitalis enhances the automaticity of cardiac cells. The increased automaticity and the alterations in conduction
velocity are the main factors underlying cardiac-arrhythmias due to digitalis intoxication (Smith and Braunwald 1980, Wilkerson 1981).

Digitalis also exerts a vagotonic effect on the heart. The decrease in conduction velocity and the prolongation of the refractory period can partly be attributed to this effect (Braunwald 1980, Hoffman and Bigger 1980, Wilkerson 1981).

3.2.1.3. Haemodynamic effects

Digitalis glycosides clearly augment the contractile force of failing and non-failing myocardium (Smith and Braunwald 1980). However, cardiac output is usually increased only in patients with heart failure. The improved myocardial performance diminishes the high sympathetic tone associated with the failure. Secondary to this, heart rate and peripheral vascular resistance fall. In spite of the fall in heart rate, cardiac output is usually increased due to the augmented contractility and the reduced vascular resistance. However, an increase in cardiac output is not always seen (Balcon et al. 1968, Cohn et al. 1975). Generally the increase in cardiac output and a simultaneous fall in venous return decrease ventricular end-diastolic pressure and volume and thereby help to relieve pulmonary congestion (Smith and Braunwald 1980). In the failing heart digitalis decreases myocardial oxygen consumption even though contractility and cardiac output are increased. This effect can be explained by the reduced heart rate and by the fall in the ventricular wall tension (Wilkerson 1981).

In compensated heart failure digitalis does not increase cardiac output but may help to maintain it at the normal level. In other words, digitalis may provide a greater inotropic reserve. The therapeutic or prognostic value of this principle is not clear. Nevertheless, it has been postulated that digitalis might improve exercise performance in patients who have impaired cardiac output on exertion although it is still normal at rest (Smith and Braunwald 1980).

In the absence of heart failure cardiac output remains unchanged or slightly declines due to peripheral arteriolar vasoconstriction and resultant increase in peripheral vascular resistance. The patient will then not benefit from the administration of digitalis (Smith and Braunwald 1980, Haustein 1983). The therapy may even be harmful because of reduced cardiac output and needless increase in myocardial oxygen consumption (DeMots et al. 1978).

Digitalis glycosides promote diuresis in patients with heart failure. The diuretic action results predominantly from the haemody-
namic improvement. A direct diuretic action of digitalis has also been shown, but only after relatively high doses. The direct effect, therefore, seems to be clinically unimportant (Hayward and Hamer 1979).

3.2.2. Side effects and toxicity

The therapeutic ratio of digitalis is very narrow. Animal studies have shown that the lethal dose is only twice the dose which leads to earliest toxic manifestations (Hayward and Hamer 1979).

Several factors may reduce the tolerance of the patient to digitalis glycosides. The risk of digitalis toxicity increases with advancing age because of deteriorating renal, pulmonary and neural function, more severe heart disease and increased number of concurrently administered drugs (Smith and Braunwald 1980). In addition, lean body mass, the principal body pool of digitalis, falls with increasing age (Taggart and McDevitt 1980, Peters 1982). Because of decreased renal excretion of the glycosides, digoxin in particular, patients with renal insufficiency have an increased risk of digitalis toxicity. An ischaemic or damaged myocardium is more sensitive to digitalis than a healthy one (Smith and Braunwald 1980). Potassium depletion is perhaps the most common precipitating factor of digitalis intoxication. Patients with heart failure are at particular risk to develop hypokalaemia due to secondary hyperaldosteronism and diuretic therapy. Hypomagnesaemia, hypercalcaemia, hypoxia and acidosis may also potentiate digitalis toxicity (Hoffman and Bigger 1980, Fenster and Marcus 1982).

Digitalis toxicity frequently manifests as various disturbances of cardiac rhythm ranging from apparently harmless extrasystoles to life-threatening tachyarrhythmias or conduction defects. Toxic arrhythmias may occur with or without preceding extracardiac manifestations of toxicity (Smith and Braunwald 1980).

Most of the extracardiac toxic symptoms of digitalis overdose result from stimulation of the central nervous system (Lely and Enter 1970, 1972). They include headache, weakness, dizziness, confusion, psychosis and even convulsions. Various visual disturbances may occur, including disturbed colour vision. Gastrointestinal symptoms including nausea, vomiting, diarrhea and anorexia may partly be due to direct irritation but more likely result from actions on the central nervous system (Hayward and Hamer 1979).

Patients with clinical digitalis toxicity have generally higher serum digitalis concentrations than patients without toxicity (Smith et al. 1969). However, there has been marked overlap of serum digitalis concentrations between toxic and non-toxic patients.

3.2.3. Pharmacokinetics

The absorption of oral digoxin shows marked interindividual variation. About 60-80% of digoxin in tablet formulation is absorbed from the gastrointestinal tract (Doherty 1981, Fenster and Marcus 1982, Peters 1982). After oral administration, a peak serum digoxin concentration is reached within one hour. Food intake and drugs that delay gastric emptying may reduce the rate of absorption but they do not affect the total amount absorbed. After absorption digoxin is distributed to tissues and bound to tissue proteins. An equilibrium between plasma and tissues is reached in about 6 hours (Fenster and Marcus 1982). Thus, to represent the slow elimination phase, blood samples for the measurement of serum digoxin concentrations should be taken at least 6 hours after the previous digoxin dose (Taggart and McDevitt 1980, Aronson 1983). The highest concentrations of digoxin have been found in the heart, kidney, liver and muscle (Fenster and Marcus 1982).

Digoxin is primarily eliminated unchanged by renal glomerular filtration with a half-life of 26-45 hours (Iisalo 1977, Fenster and Marcus 1982). The clearance of unbound digoxin roughly corresponds to creatinine clearance. Thus, the half-life of digoxin is prolonged in patients with impaired renal function. Usually only a small fraction of digoxin is metabolized in the liver and excreted in the urine. A decline in liver function does not noticeably alter the excretion (Iisalo 1977).

3.2.4. Interactions

Concomitant drug therapy may affect the actions of digitalis glycosides in many ways. Thiazide and loop diuretics may cause hypokalaemia and hypomagnesaemia which sensitize the myocardium to digitalis (Smith and Braunwald 1980). Anion exchange resins, antacids and metoclopramide may reduce oral absorption of digitalis glycosides, whereas antibiotics and anticholinergic drugs may have the opposite effect (Manninen et al. 1973, Binnion 1978, Brown et al. 1980, Lindenbaum et al. 1981). Quinidine increases serum digoxin concentration mainly due to decreased renal clearance of the glycoside (Ejvinsson 1978, Doering 1979, Reiffel et al. 1979, Brown et al. 1980, Bussey 1982, 1984). Spironolactone produces a marked increase in serum digoxin concentration (Waldorff et al. 1978,

3.3. Utilization of digitalis glycosides

3.3.1. Historical remarks

The beneficial effect of digitalis in the treatment of dropsy was first reported by Withering in 1785 (An account of... 1937). At that time digitalis was merely regarded as a diuretic. Withering was not aware of the specific cardiac actions of digitalis although he knew that the heart was somehow affected by the drug. He was, however, very well aware of the manifestations of digitalis toxicity and the necessity to dose the drug individually.

The action of digitalis on the heart was probably first recognized by Ferrier in 1799 (Hoffman and Bigger 1980) followed by Bouillaud, who in 1835 observed the sedative action of digitalis on rapid irregular pulse (McMichael 1972, Haustein 1983). In the 1870's Balfour and Fothergill first observed that digitalis increased ventricular contraction and in the beginning of the 20th century Mackenzie was the first to show that digitalis slows the ventricular response in atrial fibrillation (Willius and Keys 1961, McMichael 1972, Haustein 1983). During the second quarter of this century Wiggers and Stimson (in 1927) and Cattel and Gold (in 1938) demonstrated that digitalis glycosides exert a positive inotropic action on the heart (Smith and Braunwald 1980, Haustein 1983). At the same time, on the basis of clinical comparisons between cardiac patients with sinus rhythm and atrial fibrillation, it was concluded that digitalis had beneficial effects in both of these patient groups (McMichael 1972, Guz and McHaffie 1978). Subsequent haemodynamic studies then showed a positive inotropic action both in the normal and in the failing heart (Smith and Braunwald 1980, McMichael 1982). These observations have led many textbooks to consider digitalis the mainstay of the treatment of heart failure, disregarding cardiac rhythm (Braunwald 1980, Hoffman and Bigger 1980, Smith and Braunwald 1980, Fishman 1982). However, the usefulness of digitalis in the long-term management of heart failure in patients with sinus rhythm has recently been repeatedly questioned (Editorial 1979, Taggart and McDevitt 1980, Hamer 1982, Fleg and Lakatta 1984).
3.3.2. Indications for clinical use

3.3.2.1. Atrial fibrillation

In uncontrolled atrial fibrillation the ventricular response to the erratic atrial impulses is usually 140–200 beats per minute at rest and even higher during exercise (Bigger 1980). The excessive ventricular rate results in distressing symptoms and reduces cardiac work capacity and may lead to overt heart failure. Although the ultimate therapeutic goal is to restore sinus rhythm whenever possible, usually the fast ventricular rate first needs to be controlled. Because digitalis slows AV nodal conduction, it is the drug of choice for this indication. Digitalis only rarely converts atrial fibrillation to sinus rhythm. Generally other antiarrhythmic drugs or electrical cardioversion are required for this. After successful restoration of sinus rhythm digitalis therapy usually is maintained in order to prevent the arrhythmia from recurring, particularly if it was due to chronic heart disease. Even if the arrhythmia does recur, maintenance digitalis therapy may still be useful because of its ability to control the excessive ventricular rate often associated with the arrhythmic attack. If the fibrillation persists, digitalis therapy is indicated as long as it is necessary to reduce the ventricular rate (Bigger 1980, Hoffman and Bigger 1980).

Digitalis is contraindicated in atrial fibrillation associated with the Wolff-Parkinson-White syndrome, because it may shorten refractoriness in the anomalous AV-connection and increase ventricular rate and even cause ventricular fibrillation (Bigger 1980).

3.3.2.2. Atrial flutter

In untreated atrial flutter the AV conduction block is usually 2:1 and therefore with an atrial rate of about 300 cycles per minute the ventricular rate will be about 150 beats per minute. As in atrial fibrillation, such a fast ventricular rate needs to be controlled. Atrial flutter is less stable than atrial fibrillation and, contrary to this, can often be converted to sinus rhythm with digitalis. Digitalis sometimes converts atrial flutter to atrial fibrillation. Even if sinus rhythm is not restored, the conversion to atrial fibrillation is helpful because the ventricular rate then is more easily and reliably controlled. However, even if atrial flutter persists, digitalis is the drug of choice, since it increases the grade of the AV block and thus reduces the ventricular rate (Bigger 1980, Hoffman and Bigger 1980).
3.3.2.3. Supraventricular tachycardia

Digitalis can be used to prevent paroxysmal supraventricular tachycardias once they have been converted to sinus rhythm with other therapeutic measures. However, maintenance therapy is only rarely needed because the arrhythmia commonly occurs in normal subjects who can tolerate the symptoms until an occasional attack is terminated, frequently by simple vagal manoeuvres. Long-term therapy is indicated if attacks are frequent or tend to cause disabling symptoms or rapidly lead to haemodynamic deterioration (Bigger 1980).

3.3.2.4. Heart failure

Traditional views

According to leading textbooks of pharmacology, internal medicine and cardiovascular medicine (Braunwald 1980, Hoffman and Bigger 1980, Smith and Braunwald 1980, Fishman 1982) congestive heart failure is the main indication for digitalis glycosides. A combination of congestive heart failure and atrial fibrillation is the most apparent indication. The textbooks, however, state that equally significant results are obtained in heart failure with normal sinus rhythm. Patients with heart failure due to chronic ischaemic heart disease, arterial hypertension or valvular heart disease are likely to benefit most from digitalis therapy (Braunwald 1980). Digitalis is considered of potential value in cardiomyopathies and cor pulmonale. Little benefit from digitalis can be expected if the failure is secondary to myocardial disease caused by metabolic deficiency states, poisons or active infection (Hoffman and Bigger 1980). Similarly, digitalis is of little benefit in isolated mitral stenosis with sinus rhythm, in constrictive pericarditis and in hypertrophic subaortic stenosis (Smith and Braunwald 1980). If the failure is associated with infection, anaemia or thyreotoxicosis digitalis may be useful, although it is more important to aim the therapy at the primary disease (Hoffman and Bigger 1980).

The traditional approach is that even if a state of compensation has been achieved digitalis therapy is continued indefinitely in order to prevent the heart failure from recurring (Hoffman and Bigger 1980, McMichael 1982, Storstein 1982). This is, however, considered unnecessary if the heart failure is caused by a temporary illness which can be corrected. For instance, temporary heart failure may be associated with an acute myocardial infarction, a correctable valvular heart disease or arterial hypertension re-
sponding favorably to antihypertensive therapy (Hoffman and Bigger 1980).

Alternative views

Opie (1980) notes that "indications for digitalis are shrinking". Although, in his opinion, the combination of congestive heart failure and atrial fibrillation still is the major indication for digitalis (Opie 1980, 1984), the introduction of modern diuretics and vasodilators has lessened the need for digitalis in heart failure with sinus rhythm. Opie suggests that in the presence of sinus rhythm the treatment should be started with a diuretic (or sometimes with a vasodilator). These views have been shared by several other authors (Rubin et al. 1972, Cohn 1974, Guz and McHaffie 1978, Lemberg 1978, McHaffie et al. 1978, Editorial 1979, Hutcheon et al. 1980, Taggart and McDevitt 1980, Zatuchni 1980, Selzer 1981, Firth 1982, Poole-Wilson 1984).

Although digitalis has been shown to improve ventricular function in heart failure both at rest and during exercise (Carliner et al. 1974, Hoeschen and Cuddy 1975, Vogel et al. 1977, Arnold et al. 1980), the benefits of chronic stimulation of the heart have not been established (Lejemtel and Sonnenblick 1984). As stated by Beeson (1980) the mere demonstration that digitalis can increase cardiac efficiency does not justify giving the drug to anyone who has had heart failure. Several authors have suggested that patients receiving digitalis should be evaluated periodically to decide whether the drug is still needed (Fonrose et al. 1974, Taggart and McDevitt 1980, Carlson et al. 1985). Indeed, many investigators have reported successful withdrawal of maintenance digitalis therapy in more than half (48-94%) of patients with sinus rhythm (Fonrose et al. 1974, Hull and Mackintosh 1977, Johnston and McDevitt 1979, Krakauer and Petersen 1979, Pedersen 1979, Henning and Tanggaard 1980, Boman et al. 1981, Hartling et al. 1982, Boman 1983a). A successful withdrawal has been particularly likely in patients in a stable clinical state and with a low serum digitalis concentration (Liverpool Therapeutics Group 1978, Johnston and McDevitt 1979, Boman 1983a).

The discontinuation trials have been criticized for deficiencies in design, notably insufficient documentation of the initial indications for digitalis, variable (relatively short) periods of follow-up and lack of haemodynamic measurements (Storstein 1982, Murrow et al. 1984). Nevertheless, even if open to criticism the studies clearly have shown that many patients can manage without the long-term digitalis therapy they have been receiving. The length of the observation period is debatable. The longer the
period, the greater the risk of new episodes of heart failure that might benefit from digitalis therapy (Boman et al. 1981).

The two most obvious reasons for a successful withdrawal of digitalis are:

1. The initial indications for digitalis may have been inadequate.

2. The initial indications for digitalis may have disappeared.

In fact, as noted by Taggart and McDevitt (1980), some patients may have never been prescribed adequate doses, so that the drug probably never was having a pharmacological effect and some patients themselves may have already withdrawn the drug through noncompliance.

Recently, Murray et al. (1982) demonstrated a beneficial haemodynamic response to long-term digitalis during exercise but not at rest. In the study by Gheorghia and Beller (1983) digitalis withdrawal had no adverse clinical or haemodynamic effect at rest or during exercise in any of the patients studied. It should be noted that the patients had well documented heart failure secondary to ischaemic heart disease and that almost all of them were receiving diuretics and/or vasodilators.

The need for maintenance digitalis therapy in patients with sinus rhythm and documented previous heart failure has also been studied in double-blind placebo-controlled crossover trials (Fleg et al. 1982, Lee et al. 1982, Taggart et al. 1983). The study by Lee et al. (1982) demonstrated that the long-term use of digitalis had clinically beneficial effects in patients whose failure persisted despite diuretic treatment. No further clinical improvement, however, could be shown in patients whose left atrial pressure had been restored to normal or nearly normal by diuretic treatment. In the study by Fleg et al. (1982) no clinical deterioration occurred when chronic digitalis treatment was changed to placebo for three months. Most of the patients were receiving diuretics during the study. Similarly, Taggart et al. (1983) could not show any benefit from digitalis in most of their patients with definite traditional indications for the treatment.

Even though the long-term digitalis therapy may be of no haemodynamic benefit to most of the patients with stable cardiac state and sinus rhythm, the therapy may be needed to prevent atrial fibrillation (Johnston and McDevitt 1979, Boman 1983a).

Thus, some patients with heart failure and sinus rhythm apparently need maintenance digitalis therapy, whereas others may not require it (Chamberlain 1985, Editorial 1985). The conflicting results
might be explained by differences in the etiology and severity of the heart failure and by variable use of other drugs, most notably diuretics and vasodilators (Fleg et al. 1982, Gheorghide and Beiler 1983, Fleg and Lakatta 1984).

3.3.2.5. Prophylactic use

The value of digitalis in prophylactic use is not certain. Digitalis may increase the inotropic reserve in patients with heart disease but still without heart failure. It is, however, not known whether this therapy has any prognostic significance or whether it can prevent or retard the development of heart failure (Smith and Braunwald 1980). The role of prophylactic administration of digitalis before surgical procedures also remains unclear (Smith and Braunwald 1980). In the absence of heart failure or cardiomegaly digitalis increases myocardial oxygen consumption and may therefore provoke or aggravate myocardial ischaemia and angina pectoris in patients with coronary heart disease. For the same reason digitalis may be harmful in patients with acute myocardial infarction, if not in actual failure (Smith and Braunwald 1980). Digitalis may even increase mortality following acute myocardial infarction (Moss et al. 1981). However, the excessive mortality in patients treated with digitalis may be explained by confounding variables that correlate both with mortality and the indications for prescribing digitalis (Bigger et al. 1985).

3.3.3. Dosage and plasma concentrations

Because cardiac glycosides are rapidly absorbed from the gastrointestinal tract, the drugs are usually given orally. For adults the suggested maintenance dose of digoxin is in the range of 0.125 and 0.75 mg per day (Aronson and Grahame-Smith 1976, Hoffman and Bigger 1980, Johnston 1980, Fenster and Marcus 1982). The recommended average maintenance dose of digitoxin is 0.05-0.2 mg and that of lanatoside C 0.25-1.5 mg per day (Hoffman and Bigger 1980). With the maintenance dose of digoxin it takes 5-7 days to reach a steady state concentration in plasma and tissues (Smith 1973, Braunwald 1980). The therapy has therefore been traditionally started with a loading dose. For adults the loading dose of digoxin has been 0.5-1.5 mg in divided doses over 24 hours (Johnston 1980, Fenster and Marcus 1982). However, to avoid toxicity, it is now more customary to start the therapy with the maintenance dose.

The average actual dose of digoxin has been close to 0.25 mg/day in most reports (Bergman et al. 1976, Landahl et al. 1977, Liverpool Therapeutics Group 1978, Weintraub et al. 1979, Johnston and McDevitt 1980, Bergman et al. 1981, Holmberg and Böttiger 1983).
Generally a reduced dose is prescribed for the elderly (Weintraub et al. 1979, Holmberg and Böttiger 1983).

The dosage is problematic because of the narrow therapeutic ratio and the widely variable response between individuals. In atrial fibrillation the dose can be adjusted to attain the desired ventricular rate but in sinus rhythm no corresponding therapeutic objective can be set (Taggart and McDevitt 1980, Selzer 1981, Cownihan 1982). To help dosing several prescribing aids have been tried but often with disappointing results (Peck et al. 1973, Dobbs et al. 1977, 1978, Aronson 1978, Johnston et al. 1979, Johnston 1980).

Measurement of plasma (serum) digitalis concentration may help to individualize the therapy and to diagnose or prevent digitalis toxicity, especially in patients with sinus rhythm (Smith et al. 1969, Beller et al. 1971, Duhne et al. 1974, Smith 1975, Huffman et al. 1976, Holt et al. 1977, Aronson 1980, Taggart and McDevitt 1980). The measurements can also be used to indicate poor patient compliance (Weintraub et al. 1973, Sheiner et al. 1974, Gundert-Remy et al. 1976, Johnston and McDevitt 1978, Johnston et al. 1978), which the physician may not be able to confirm or predict otherwise (Gilbert et al. 1980).

Although there is not a linear relationship between plasma digitalis concentration and therapeutic or toxic effects, plasma digoxin concentrations below 0.8 ng/ml have generally been considered subtherapeutic, whereas those over 2.0 ng/ml are thought to be associated with increasing risk of toxicity (Koch-Weser 1972, Whiting et al. 1973, Huffman et al. 1976, Aronson 1981). Plasma digoxin concentrations about 0.8-2.0 ng/ml have therefore been considered "therapeutic" (Taggart and McDevitt 1980, Aronson 1983, Hoffman and Bigger 1980). In patients receiving lanatoside C the concentrations can be measured by the digoxin assay (Fenster and Marcus 1982) and therefore the therapeutic range given for digoxin applies to lanatoside C as well.

Several reports have shown that many patients undergoing maintenance digoxin therapy have serum steady state digoxin concentrations below the recommended therapeutic range. For example, in a Finnish study, in about 40% of the patients the concentration was below 0.5 ng/ml (Iisalo and Schrey 1977). On the other hand, the concentration exceeded 2.0 ng/ml in only 1%. Similar results have been reported from other countries. In the study by Bergman et al. (1976) 62% of the patients had serum digoxin concentrations below 1.0 ng/ml and in only 3% the concentration was over 2.0 ng/ml. In the study by Landahl et al. (1977) 30% of the digoxin-treated patients had serum digoxin concentrations below 0.5 nmol/l (0.4 ng/ml). In this study the concentration exceeded the upper limit of 2.9 nmol/l (2.2 ng/ml) in 10% of the patients.
In a German study (Bodem et al. 1979) 57% of patients taking digitalis had plasma concentrations within the therapeutic range. In Liverpool (Liverpool Therapeutics Group 1978) the serum digitalis concentration was subtherapeutic in about 40% of the patients. In about 10% it was above the therapeutic range.

Digoxin immunoreactivity assigned to an as yet uncharacterized "endogenous digoxin-like immunoreactive factor" has been reported in plasma from subjects not receiving the drug. The nature and physiologic role of this factor remain obscure (Valdes 1985). Its very existence has been in some doubt (Wilkins 1985). Such a factor in human plasma might confound the interpretation of digoxin measurements. However, the values are usually below the detection sensitivity (<0.2 ng/ml) of a conventional immunoassay except in newborn infants, pregnant women and some patients with hepatic or renal failure (Valdes 1985).

3.3.4. Occurrence of digitalis toxicity

Digitalis toxicity has been reported to be common. The estimates vary according to study populations and criteria for toxicity. Taggart and McDevitt (1980) note that in various materials toxic reactions have been diagnosed in 4–35% of hospitalized patients receiving digitalis. Smith and Braunwald (1980) estimate that 5–15% of hospitalized patients on digitalis suffer from digitalis intoxication. In the study by Beller et al. (1971), judged by serial electrocardiograms, 29% of all patients with digitalis therapy had digitalis toxicity on admission to hospital. Digitalis toxicity is frequently the reason for admission to hospital. For example, in the study by Holmberg and Böttiger (1983) about 7% of the admissions of digoxin-treated patients were due to toxicity. The prevalence of digitalis toxicity is therefore likely to be higher in hospitalized than among ambulatory patients. In an unselected Swedish patient series intoxication was definitely diagnosed in 5% and suspected in 2% of all patients on digitalis therapy (Boman and Möllerberg 1979). The incidence of suspected digitalis toxicity in an outpatient population was recently estimated at 5 episodes per 100 patient-years at risk (Carlson et al. 1985).

3.3.5. Extent of use in various populations

3.3.5.1. Records of drug distributors

To compare pharmacy sales of digitalis in various populations the following defined daily doses (DDD) have been applied: digoxin 0.25 mg, digitoxin 0.1 mg, lanatoside C 1 mg and proscillaridin A
0.75 mg (Nordic Statistics on Medicines 1982b). In 1980 the Finnish sales of all cardiac glycosides were 42.18 DDD/1000 inhabitants/day. In Nordic comparison the sales are clearly the highest in Finland (Fig. 1), especially if it is taken into account that unlike the others the Finnish statistics do not include direct sales to hospitals (Nordic Statistics on Medicines 1982a). In Sweden the sales to hospitals have amounted to about 7% of the annual total sales of digitalis (Dahlström et al. 1978). Digoxin is the preferred glycoside in the Nordic countries, with the exception of Norway, where digitoxin dominates. Digoxin comprised 95.1% of all glycosides sold in Finland in 1980 (Nordic Statistics on Medicines 1982a).

![Fig. 1. Sales of cardiac glycosides in the five Nordic countries in 1980 (DDD = defined daily dose).](image)

So far, the Finnish sales figures of cardiac glycosides seem to be exceeded only by those of the Federal Republic of Germany (64.29 DDD/1000 inhabitants/day in 1978). Much lower figures have been reported from several other European countries, such as Great Britain (10.16), France (8.81) and Spain (7.29). Thus, within Europe the highest sales figure seems to be at least nine times the lowest (Friebel 1982).

The sales statistics have shown marked variation in glycoside utilization even within countries. For example, in Sweden the sales figures have been reported to vary from 29 to 61 DDD/1000 inhabitants/day between regions (Dahlström et al. 1978, Boman and Ögren 1981). In Czechoslovakia the wholesale statistics have shown a 2.5-fold consumption of cardiac glycosides in the Czech Socialist
Republic as compared with that of the Slovak Socialist Republic (Stika et al. 1979).

3.3.5.2. Prescriptions

Reports on digitalis prescriptions are scarce. An analysis of information received from the drug industry in the United Kingdom showed that digitalis is prescribed mainly for people over 65 years of age (Tunstall-Pedoe 1978). According to this study a total of 600,000 patients (including 6% of those over 65) were receiving lanoxin or unbranded digoxin, the predominant glycosides in the U.K. The main indication for prescribing digitalis in that study was heart failure (in 44%). Other indications included disorders of rhythm in 15%, ischaemic heart disease in 10%, valvular heart disease in 4% and other diagnoses in 7%. The diagnosis was not available in 20% of the patients.

3.3.5.3. General practice and hospital records

Hull and Mackintosh (1977) report that 300,000 people receive digoxin in the U.K. In their own practice 24 of 4630 patients (0.5%) were on digoxin. Only 6 of these were in atrial fibrillation. In the practice of Bethell (1977) 44 (1.5%) out of 3000 patients were receiving digoxin. Supraventricular tachycardia was the apparent indication for the drug in 29 of the 44 patients.

Of patients acutely admitted to two Swedish medical clinics 23-30% were receiving digitalis glycosides (Bergman and Wiholm 1981, Holmberg and Böttiger 1983). The proportion of patients taking digitalis increases steeply with advancing age. In the study by Holmberg and Böttiger (1983) it was about 20% at the age of 50-59 and 60% in the age-group of 80 or over.

In a Swedish university hospital 26% of the hospitalized medical patients were on digitalis (Bergman et al. 1981). In about 80% the indication for prescribing digitalis was heart failure. In the Federal Republic of Germany about 41% of all medical in-patients in a university hospital were receiving digitalis, 30% digoxin or its derivates and 11% digitoxin (Czechanowski et al. 1983). About 22% of the hospitalized medical patients in three Boston hospitals were receiving digitalis (Shapiro et al. 1969). In this study the main indication for giving the drug was heart failure (85% of all). In 6.6% the indication was cardiac arrhythmia.

Digoxin therapy was observed in 13.8% of out-patients and 16.4% of in-patients in a Danish geriatric study (Krakauer and Petersen
1979). In a Swedish geriatric in-patient population the prevalence of digoxin use was 28% (Boman 1983b).

3.3.5.4. Consumer surveys

Few consumer surveys, restricted to certain age groups or geographical areas, have been carried out. In a rural community in South-west Finland about 1% of men and 2% of women aged 41-60 years reported the use of digitalis (Tuomi 1965). In a remote low density population area in Sweden Bergman et al. (1976) examined all patients more than 60 years of age who were receiving digitalis (digoxin). The patients amounted to 3% of the population. Heart failure had been diagnosed in 96% of the patients. Atrial tachyarrhythmias (with or without heart failure) had been diagnosed in 8% of the patients.

Among 70-year-old people in Gothenburg the prevalence of digitalis use was found to be 14%, 6% taking digoxin, 6% digitoxin and 2% other glycosides (Landahl et al. 1977).

Seven per cent of the 30-69 year-old population of Munich were taking digitalis glycosides, mostly digoxin or its acetyl or methyl derivates (Koenig et al. 1984). Two thirds of those on digitalis were over 60 years of age. Sinus rhythm was present in 93%.

To the author's knowledge no surveys on the utilization of digitalis glycosides have been carried out in nationwide representative population samples.
4. AIMS OF THE STUDY

The general object of the present work was to study the utilization of digitalis glycosides in Finland using information collected in a comprehensive health interview and examination carried out in a representative sample of the Finnish population aged 30 years or over.

More specific aims of the study were:

1. to estimate the prevalence of digitalis use and the number of digitalis users
2. to study the regional variation in the prevalence of digitalis use within the country
3. to study the short-term and long-term variation in reported use of digitalis
4. to estimate the extent of possible overuse and underuse of digitalis
5. to study the level and variation of serum digoxin concentrations in those receiving digoxin, the dominant digitalis glycoside in Finland
6. to study how digitalis therapy is generally practised and controlled.
5. STUDY POPULATIONS AND METHODS

The study was part of the Mini-Finland Health Survey of the Social Insurance Institution. This survey was carried out in 1977-1980 in a representative sample of the Finnish population aged 30 years or over. Details of the study populations and the survey methods have been published elsewhere (Aromaa et al. 1985) and will therefore be only briefly described here. The survey consisted of a health interview followed by a health examination in two phases, a screening phase and a re-examination phase (Fig. 2).

5.1. Study populations

The study population proper was a stratified two-stage cluster sample selected to represent the Finnish population aged 30 years or over. The sample was drawn from the population register of Finland, excluding the Åland Islands.

In the first stage 320 clusters of municipalities were formed and stratified with regard to geographical area (social insurance region), degree of urbanization and proportions of people employed in industry and agriculture. The clusters were arranged in 40 strata and one cluster was selected from each stratum with a probability proportional to the size of the population in the cluster.

In the second stage the subjects were selected with systematic sampling from the 40 clusters in proportion to the relative population size of each cluster. The sample size was 8000, 195 of whom were in long-term institutional care. Table 1 shows the sample by sex, age and social insurance region. Fig. 3 shows the selected clusters (study areas) spread over the five social insurance regions.

A separate population sample of 600 people aged 30-69 years served to assess the long-term variability of a number of measurements. This sample was drawn at random from the population register of the city of Turku.
Fig. 2. Phases of the Mini-Finland Health Survey and the main sources of information on the utilization of digitalis.
Fig. 3. The study areas of the Mini-Finland Health Survey and the social insurance regions of Finland.
Table 1. The population sample of the Mini-Finland Health Survey by sex, age group and social insurance region

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5.2. Survey methods

The health interviews were carried out by local public health nurses who visited the subjects a few weeks before the health examination. The interview comprised questions concerning current use of prescribed drugs (Appendix 1). The reported drugs were checked from prescriptions or package labels.

The health examinations were carried out by the mobile clinic unit of the Social Insurance Institution. With the invitation to attend the screening phase of the health examination the subjects received a basic questionnaire including questions on chronic cardiovascular diseases diagnosed by a doctor and current and recent use of prescribed drugs (Appendix 2). The subjects were asked to bring along the prescriptions for the drugs they had been taking during the previous 12 months. No prior information about the plans to study the utilization of drugs was given. Specially trained nurses reviewed the questionnaires and the prescriptions and recorded all drugs used by the subjects during the previous 3 months. For each of these drugs it was further recorded whether it was in regular
or temporary use and whether the subject had taken it within the 7 and 2 preceding days.

If a record was made of the use of a digitalis glycoside, the nurses continued with a special digitalis interview inquiring about the trade mark, strength and dosing schedule of the drug (Appendix 3). The dose and the time of the latest ingestion of the drug were also recorded in this interview.

A blood sample was drawn for radioimmunologic determination of serum digitalis concentration (Smith et al. 1969). The exact time of blood sampling was recorded and the interval between the sampling and the latest ingestion of digitalis was calculated.

The method for the measurement of serum digoxin concentrations has been described in detail by Allonen et al. (1975) and by Allonen (1978). The detection limit of the assay was about 0.2 ng/ml (Allonen 1978). At the level of 0.5 ng/ml the intra-assay accuracy was 90 % and the coefficient of variation 9 %. At the level of 2.0 ng/ml the corresponding figures were 112 % and 4 % (Allonen 1978). The mean inter-assay accuracy was 100 % at the level of 1.5 ng/ml (III) and 101 % at the level of 2.0 ng/ml (Allonen 1978). The inter-assay coefficient of variation was 5 % at the level of 1.5 ng/ml (III) and 8 % at the level of 2.0 ng/ml (Allonen 1978). The specificity of the assay was also studied by Allonen (1978). Digoxin and methyldigoxin were similarly bound to the antiserum. Digitoxin and dihydridigoxin did not appreciably interfere with the assay, whereas the digoxigenin metabolites of digoxin were moderately bound to the antiserum. There was no interference of steroid hormones or spironolactone with the assay (Allonen et al. 1975).

If the participant reported in the basic questionnaire that he/she had been diagnosed by a doctor as suffering from an organic cardiovascular disease or was taking nitroglycerin or digitalis, a supplementary cardiovascular disease interview was carried out. This interview included questions about the physician responsible for the care, the frequency of consultations and an estimate (by the nurse interviewer) of the continuity of the care (Appendix 4).

The methods of the screening phase also comprised a standard chest X-ray and an electrocardiogram. Two clinical radiologists measured relative heart volumes by standard contrast medium technique and the mean value of the two independent measurements was used to evaluate cardiac state. The electrocardiograms were analyzed by a computer programme (Pipberger et al. 1975) and all abnormal recordings were reviewed by experienced physicians before final ECG-diagnoses were made.
According to the general design of the Mini-Finland Health Survey all participants with a history or with symptoms or signs suggesting any major organic cardiovascular disease were invited to the re-examination, which took place about 3 months after the screening phase. Among others, all those who had received digitalis during the preceding 3 months were invited. This time they were asked not to take digitalis on the morning of the examination day. In the re-examination the digitalis interview was repeated and a second blood sample was drawn for serum digitalis radioimmunoassay.

A postal inquiry including questions on prescribed drugs was sent to all those who did not attend the health examination (Appendix 5).

The repeatability of the basic questionnaire (including questions on drug use) and the variation in reported use of digitalis was estimated in a random 20% subsample of those who had participated in the screening phase. The questionnaire was repeated in this subsample in the re-examination phase. The long-term repeatability (variation) was estimated at yearly intervals (one and two year follow-ups) in the separate population sample drawn for this purpose.

5.3. Participation in the survey

Tables 2 and 3 show the participation rates for the health interview and for the screening examination, respectively. Altogether 7703 persons (96.3% of the sample) participated in the former and 7217 (90.2% of the sample) in the latter.

Table 2. Participation in the health interview

<table>
<thead>
<tr>
<th>Age group</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% of sample</td>
</tr>
<tr>
<td>30 - 44</td>
<td>1387</td>
<td>95.9</td>
</tr>
<tr>
<td>45 - 54</td>
<td>819</td>
<td>97.5</td>
</tr>
<tr>
<td>55 - 64</td>
<td>629</td>
<td>95.5</td>
</tr>
<tr>
<td>65 - 74</td>
<td>470</td>
<td>95.9</td>
</tr>
<tr>
<td>75 -</td>
<td>193</td>
<td>96.0</td>
</tr>
<tr>
<td>Total</td>
<td>3498</td>
<td>96.2</td>
</tr>
</tbody>
</table>
Table 3. Participation in the screening phase of the health examination

<table>
<thead>
<tr>
<th>Age group</th>
<th>Men</th>
<th>% of sample</th>
<th>Women</th>
<th>% of sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 44</td>
<td>1343</td>
<td>92.8</td>
<td>1373</td>
<td>94.6</td>
</tr>
<tr>
<td>45 - 54</td>
<td>781</td>
<td>93.0</td>
<td>828</td>
<td>93.8</td>
</tr>
<tr>
<td>55 - 64</td>
<td>603</td>
<td>91.5</td>
<td>745</td>
<td>90.7</td>
</tr>
<tr>
<td>65 - 74</td>
<td>436</td>
<td>89.0</td>
<td>642</td>
<td>84.5</td>
</tr>
<tr>
<td>75 -</td>
<td>159</td>
<td>79.1</td>
<td>307</td>
<td>68.7</td>
</tr>
<tr>
<td>Total</td>
<td>3322</td>
<td>91.3</td>
<td>3895</td>
<td>89.3</td>
</tr>
</tbody>
</table>

There were 7209 subjects (3316 men and 3893 women) who took part both in the health interview and in the screening examination and 7711 (3504 men and 4207 women) who participated in at least one of these. This left 289 persons who participated neither in the health interview nor in the screening examination. However, 117 (53 men and 64 women) of these responded to the postal inquiry. Hence, 7828 persons (97.9% of the sample) participated either in the health interview or in the screening phase or at least responded to the postal inquiry (I).

There were 791 participants who had received continuous or temporary digitalis therapy 0-3 months before the screening phase. Thus, they met at least this screening criterion and were invited to the re-examination. Table 4 shows their participation rates.

The repeatability of the basic questionnaire and the stability (variation) of the reported use of digitalis was evaluated in 1264 persons who participated both in the screening phase and in the re-examination phase. Their number equaled 90.2% of the random subsample. The long-term variation was assessed in 374 subjects after one year and in 356 after two years, representing 62.3% and 59.3% of the separate population sample, respectively (I).
Table 4. Participation of the screening positive in the re-examination phase of the health examination (screening positive = those who had received digitalis within three months before the screening phase)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening positive</td>
<td>Participated</td>
<td>Screening positive</td>
<td>Participated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td></td>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 - 44</td>
<td>5</td>
<td>5</td>
<td>100.0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>45 - 54</td>
<td>30</td>
<td>20</td>
<td>66.7</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>55 - 64</td>
<td>77</td>
<td>69</td>
<td>89.6</td>
<td>102</td>
<td>89</td>
</tr>
<tr>
<td>65 - 74</td>
<td>118</td>
<td>97</td>
<td>82.2</td>
<td>209</td>
<td>183</td>
</tr>
<tr>
<td>75 -</td>
<td>66</td>
<td>52</td>
<td>78.8</td>
<td>151</td>
<td>115</td>
</tr>
<tr>
<td>Total</td>
<td>296</td>
<td>243</td>
<td>82.1</td>
<td>495</td>
<td>416</td>
</tr>
</tbody>
</table>

5.4. Statistical methods

The statistical analyses were carried out using analysis of variance and the t-test or the chi square test (II, III, IV). Age adjustments of prevalences were performed using the direct method (Armitage 1971) either within the present study series (III, IV) or within the total Finnish population aged 30 years or over (I, II) according to the census of 1980 (Central Statistical Office... 1983). The total population of 1980 was also used to estimate the numbers of people using digitalis in the whole country (I, II). The estimates were carried out as described by Landis et al. (1982). The likelihood ratio test of a logistic model (Cox 1970) was used to test the differences in age-adjusted prevalences of various findings between men and women and between the five social insurance regions (I, IV). The same method was used to calculate relative risks of questionable or poorly controlled therapy in various classes of possible explanatory variables (IV). The repeatability of the interview and questionnaire methods employed to record digitalis use (I) was evaluated by kappa-values (Fleiss 1981).
6. SUMMARY OF THE RESULTS

6.1. Prevalence of digitalis use and number of digitalis users

Table 5 shows the prevalences of reported use of digitalis among the examinees who responded at least to the postal inquiry. Table 6, respectively, shows the prevalences of radioimmunologically proven use of digitalis among the participants in the screening phase. These prevalences (Tables 5 and 6) were calculated including institutional patients. The corresponding prevalences after the exclusion of institutional patients are shown in the original paper (1).

Table 5. Prevalence (%) of reported use of digitalis among those responding at least to the postal inquiry (n=7828, institutional patients included)

<table>
<thead>
<tr>
<th>Social insurance region</th>
<th>Age group</th>
<th>Total (age-adjusted)</th>
<th>Difference from South-west (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-44</td>
<td>45-54</td>
<td>55-64</td>
</tr>
<tr>
<td>Men (n=3557)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South-west</td>
<td>0.3</td>
<td>2.8</td>
<td>4.8</td>
</tr>
<tr>
<td>South</td>
<td>0.4</td>
<td>3.3</td>
<td>13.1</td>
</tr>
<tr>
<td>West</td>
<td>0.0</td>
<td>5.4</td>
<td>14.6</td>
</tr>
<tr>
<td>East</td>
<td>0.0</td>
<td>4.3</td>
<td>19.8</td>
</tr>
<tr>
<td>North</td>
<td>0.7</td>
<td>3.8</td>
<td>15.7</td>
</tr>
<tr>
<td>Total</td>
<td>0.3</td>
<td>3.8</td>
<td>12.5</td>
</tr>
<tr>
<td>Women (n=4271)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South-west</td>
<td>0.9</td>
<td>2.7</td>
<td>9.6</td>
</tr>
<tr>
<td>South</td>
<td>0.0</td>
<td>1.4</td>
<td>9.9</td>
</tr>
<tr>
<td>West</td>
<td>0.0</td>
<td>5.2</td>
<td>19.1</td>
</tr>
<tr>
<td>East</td>
<td>0.0</td>
<td>3.8</td>
<td>16.5</td>
</tr>
<tr>
<td>North</td>
<td>1.2</td>
<td>7.1</td>
<td>20.0</td>
</tr>
<tr>
<td>Total</td>
<td>0.4</td>
<td>3.3</td>
<td>13.3</td>
</tr>
</tbody>
</table>

Men vs women: p < 0.05
Table 6. Prevalence (%) of proven use of digitalis among the participants in the screening phase of the health examination (n=7217, institutional patients included)

<table>
<thead>
<tr>
<th>Social insurance region</th>
<th>Age group</th>
<th>Total (age-adjusted)</th>
<th>Difference from South-west (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-44</td>
<td>45-54 55-64 65-74 75-</td>
<td></td>
</tr>
<tr>
<td>Men (n=3322)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South-west</td>
<td>0.3</td>
<td>1.7     4.5 19.6 11.9</td>
<td>5.0</td>
</tr>
<tr>
<td>South</td>
<td>0.2</td>
<td>2.0     11.9 22.1 51.2</td>
<td>9.5 &lt;0.01</td>
</tr>
<tr>
<td>West</td>
<td>0.0</td>
<td>5.7     13.8 26.0 37.0</td>
<td>10.1 &lt;0.001</td>
</tr>
<tr>
<td>East</td>
<td>0.5</td>
<td>3.8     17.0 28.8 35.5</td>
<td>10.7 &lt;0.001</td>
</tr>
<tr>
<td>North</td>
<td>0.7</td>
<td>4.2     10.5 28.0 66.7</td>
<td>12.0 &lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>0.3</td>
<td>3.1     11.0 24.1 37.1</td>
<td>8.9</td>
</tr>
<tr>
<td>Women (n=3895)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South-west</td>
<td>0.9</td>
<td>2.9     8.1 22.2 37.7</td>
<td>8.4</td>
</tr>
<tr>
<td>South</td>
<td>0.0</td>
<td>0.8     7.0 22.3 41.8</td>
<td>7.7 n.s.</td>
</tr>
<tr>
<td>West</td>
<td>0.0</td>
<td>5.3     18.2 35.0 44.7</td>
<td>12.6 &lt;0.01</td>
</tr>
<tr>
<td>East</td>
<td>0.0</td>
<td>3.0     12.4 28.1 50.8</td>
<td>10.6 n.s.</td>
</tr>
<tr>
<td>North</td>
<td>0.6</td>
<td>6.3     16.9 32.8 56.0</td>
<td>13.4 &lt;0.01</td>
</tr>
<tr>
<td>Total</td>
<td>0.3</td>
<td>3.0     10.9 26.3 44.3</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Men vs women: n.s.

All the prevalences increased remarkably with advancing age (p<0.001). Including institutional patients, the age-adjusted prevalence of reported use of digitalis was 10.0 % in men and 11.5 % in women. Definitely proven use of digitalis was observed in 8.9 % of men and 9.7 % of women (I).

Based on the age-specific prevalences of reported use of digitalis in the sample, the total number of digitalis users in Finland was estimated at 311,000 (112,000 men and 199,000 women). The 95 % confidence limits of the estimate were 289,000-333,000. About 60,000 (54 %) of the men and 140,000 (70 %) of the women using digitalis were 65 or older (I).

On the basis of the age-specific prevalences of proven use of digitalis, the total number of digitalis users was estimated at 248,000 (95,000 men and 153,000 women). The 95 % confidence limits of this estimate were 227,000-269,000 (I).
About 10% of all patients using digitalis were in long-term institutional care. Excluding the institutional patients, the age-adjusted prevalence of reported use of digitalis was 9.6% in men and 11.2% in women. The prevalence of proven use of digitalis, on the other hand, was then 8.6% in men and 9.6% in women (I).

6.2. Regional variation in digitalis use

The age-adjusted prevalences of digitalis use in men and women differed significantly (p<0.001) between the social insurance regions. In men all the age-adjusted prevalences were clearly the lowest in South-western Finland. The prevalences were significantly higher in South and West Finland and still higher in East and North Finland. In women the regional differences were less marked than in men. The prevalences were about the same in South-west and South Finland. Compared with these, somewhat higher prevalences were seen in East and West Finland and higher prevalences still in the North (I).

6.3. Stability of reported use of digitalis

Table 7 compares the use of digitalis reported in the health interview, on the one hand, and in the screening phase, on the other hand. The percentage of agreement between the two examinations, separated by a median interval of 41 days, was 99.2. The kappa-value was 0.96.

Table 7. Use of digitalis as reported by the examinees who participated both in the health interview and in the screening examination (n=7209)

<table>
<thead>
<tr>
<th>Health interview</th>
<th>No digitalis</th>
<th>Digitalis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening examination</td>
<td>No digitalis</td>
<td>6389</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Digitalis</td>
<td>30</td>
<td>762</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>6419</td>
<td>790</td>
</tr>
</tbody>
</table>

% of agreement 99.2, kappa 0.96
Table 8 shows the variation in the reported use of digitalis between the screening examination and the re-examination in the random subsample. The median interval between these examinations was 115 days. In this comparison the percentage of agreement was 99.1 and the kappa-value 0.95. A closer analysis showed that 121 of the 124 patients who reported the use of digitalis in the two examinations had taken the drug within 7 days before both of these occasions. Nine out of the 10 new users of digitalis had taken the drug within 7 days. On the other hand, the one who reported the use of digitalis only in the screening phase had not taken any of it within 7 days before the examination.

Table 8. Reported use of digitalis in the random subsample (n=1264) participating both in the screening phase and in the re-examination phase

<table>
<thead>
<tr>
<th></th>
<th>Re-examination phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No digitalis</td>
</tr>
<tr>
<td>Screening phase</td>
<td></td>
</tr>
<tr>
<td>No digitalis</td>
<td>1129</td>
</tr>
<tr>
<td>Digitalis</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1130</td>
</tr>
</tbody>
</table>

% of agreement 99.1, kappa 0.95

Tables 9 and 10 show the variation in the separate population sample after one year and two years, respectively. After one year the percentage of agreement was 98.1 and the kappa-value 0.81. After two years the corresponding figures were 97.5 and 0.71.

The therapy was consistent also with respect to the specific glycosides taken. The glycoside had been changed between the screening phase and the re-examination phase only in three participants: one had been changed from digitoxin to digoxin, one from lanatoside C to digoxin and one from digoxin to proscillaridin A.
Table 9. Reported use of digitalis in the separate population sample at baseline and after one year (n=374)

<table>
<thead>
<tr>
<th></th>
<th>After one year</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No digitalis</td>
<td>Digitalis</td>
<td>Total</td>
</tr>
<tr>
<td>At baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No digitalis</td>
<td>351</td>
<td>6</td>
<td>357</td>
</tr>
<tr>
<td>Digitalis</td>
<td>1</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>352</td>
<td>22</td>
<td>374</td>
</tr>
</tbody>
</table>

% of agreement 98.1, kappa 0.81

Table 10. Reported use of digitalis in the separate population sample at baseline and after two years (n=356)

<table>
<thead>
<tr>
<th></th>
<th>After two years</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No digitalis</td>
<td>Digitalis</td>
<td>Total</td>
</tr>
<tr>
<td>At baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No digitalis</td>
<td>335</td>
<td>6</td>
<td>341</td>
</tr>
<tr>
<td>Digitalis</td>
<td>3</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>338</td>
<td>18</td>
<td>356</td>
</tr>
</tbody>
</table>

% of agreement 97.5, kappa 0.71

6.4. Estimation of overuse and underuse of digitalis

ECG-analyses showed that about 90% of digitalis users were in sinus rhythm. Moreover, almost 50% of all digitalis users not only were in normal sinus rhythm but also had a normal roentgenographic heart volume. A normal heart volume and a subtherapeutic serum digitalis concentration was found in 17.6% of the men and in 19.1% of the women with sinus rhythm (II). Table 11 shows the age-adjusted prevalences of men and women with the above findings and their estimated total numbers in the Finnish population. A subtherapeutic serum digitalis concentration in the presence of sinus rhythm and normal heart volume (suggesting overuse of digitalis) was especially common in South Finland and East Finland (IV).
Table 11. Age-adjusted prevalences and estimated numbers of digitalis users with various findings relative to cardiac state

<table>
<thead>
<tr>
<th>Finding</th>
<th>Age-adjusted prevalence (%)</th>
<th>Difference between men and women</th>
<th>Total number in Finland (with 95% confidence limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitalis in sinus rhythm</td>
<td>8.2</td>
<td>10.1</td>
<td>246,000 (225,000-267,000)</td>
</tr>
<tr>
<td>Digitalis in sinus rhythm with normal heart volume</td>
<td>4.4</td>
<td>5.2</td>
<td>129,000 (115,000-143,000)</td>
</tr>
<tr>
<td>Digitalis in sinus rhythm with normal heart volume and subtherapeutic serum digitalis concentration</td>
<td>1.4</td>
<td>1.9</td>
<td>45,000 (36,000-54,000)</td>
</tr>
</tbody>
</table>

The age-adjusted prevalence of atrial fibrillation and/or a markedly enlarged heart was 1.5% in men and 0.9% in women not taking digitalis. On the basis of age-specific prevalences the total number of such patients (showing possible underuse of digitalis) was estimated at 23,000 in the Finnish population. The 95% confidence limits of this estimate were 16,000-30,000 (II).

6.5. Level and variation of serum digoxin concentrations

There was a wide interindividual variation in serum digoxin concentrations even in patients with equal intervals between the latest dose and blood sampling (the post-dose interval).

The age-adjusted mean steady state serum digoxin concentrations were 1.02±0.53 ng/ml in men and 0.98±0.50 ng/ml in women. No significant differences were observed between the age groups, although the concentrations tended to rise with advancing age. The steady state concentration was within the recommended "therapeutic" range (0.8-2.0 ng/ml) in 59.2% of the patients. In 37.6% the concentration was subtherapeutic and in 3.2% it was above the therapeutic range (III).
The proportion of patients with subtherapeutic serum digitalis concentrations varied significantly between the five social insurance regions. Subtherapeutic concentrations were most common in the South and in the East of Finland (IV).

Fig. 4 shows the comparison of steady state serum digoxin concentrations measured in the same patients in the screening phase and in the re-examination. None of the patients had a steady state serum digoxin concentration above 2.0 ng/ml in both measurements. There was a good correlation between the measurements \((r=0.57; \ p<0.001)\). The mean concentration was 1.00±0.52 ng/ml in the screening phase and 1.06±0.50 ng/ml in the re-examination. The correlation between the serum digoxin concentrations in the two examinations was very little influenced by the post-dose interval, at least in the range of 0-41 hours. There was virtually no correlation \((r=0.02)\) between the change in serum digoxin concentration and the change in post-dose interval between the two examinations (III).

![Graph](image)

**Fig. 4.** Correlation and regression line with 95% confidence limits of serum digoxin concentrations measured in the screening phase and in the re-examination phase in 260 patients. The patients were examined on both occasions 7-41 hours after their last digoxin dose. Daily digoxin dose was unaltered. \(R = 0.57\). Regression equation \(Y = 0.59 \times X + 0.38\).
6.6. Practice and control of digitalis therapy

Over 90% of the patients undergoing maintenance digitalis therapy were taking digoxin, most commonly 250 μg or 125 μg once daily. Few patients were receiving digitalis as the sole prescribed drug. The mean number of prescribed drugs was 4.2±2.0 for men and 4.6±2.1 for women undergoing maintenance digitalis therapy (p<0.05). Some of the patients were taking at least 10 prescribed drugs simultaneously (IV).

In rural areas over 80% of the patients on digitalis therapy were under the care of the local health centre. In contrast, only half of the urban patients consulted the health centre, the rest of the patients being under the care of private general practitioners or specialist or hospital outpatient clinics. About 85% of the patients generally visited their "own" doctor for the control of cardiovascular diseases. At least one visit within the previous 12 months was reported by almost 90% of the patients (IV).

A new appointment for further control of the cardiovascular therapy had been made by half of the patients receiving long-term digitalis therapy, whereas the other half was more or less uncertain when the next visit to the doctor would be (IV). A subtherapeutic serum digitalis concentration suggesting poorly controlled or questionable use of the drug was observed in about one third of the patients (III, IV). The proportions of digitalis users in poor control as well as the proportions of those with subtherapeutic serum digitalis concentrations varied significantly between the social insurance regions. The findings suggesting questionable or inadequate digitalis therapy were especially common in South and East Finland (IV).
7. DISCUSSION

7.1. Methodological aspects

The general aim of the Mini-Finland Health Survey was to provide information on the most important chronic cardiovascular, respiratory, musculoskeletal and mental diseases and disorders. Most of these generally affect middle-aged or elderly people but are relatively uncommon in the young. The lower age limit of the population sample was therefore set at 30 years. Use of digitalis was very rare below age 45 (I). Hence, the age limit did not appreciably bias the representative nature of the study.

To guarantee the representativeness of the results it is important to obtain a high response rate from the study population. In this study more than 96 % of the subjects in the sample were actually seen. In the health interview the participation rate was about the same in all age-sex groups (Table 2). In the health examination, however, the response rate was poorer than the average in those 75 or over (Tables 3 and 4). Because the use of digitalis is common in this age group, the results of the screening phase and the re-examination phase were open to a small selection bias, which may have resulted in some underestimation of the prevalence of proven use of the drug.

Overall, the response rates in this study were very high, since basic information concerning the use of digitalis was obtained from about 97.9 % of the sample (I). Nevertheless, missing information about the details of use and about the serum glycoside content, as well as missing chest X-rays and electrocardiograms somewhat reduced the number of analyzable cases. Thus, depending on what information was needed the numbers of subjects included in the analyses varied slightly between the separate papers (I-IV).

Because the study was carried out in a representative population sample and the response rate was high, the results can be generalized to the total Finnish population aged 30 or over. Moreover, since digitalis therapy turned out to be very consistent (I, III) and the participants did not know that their use of drugs was about to be studied, the results very likely represent the real state of the therapy in Finland.

A significant serum glycoside concentration is probably the best indicator of actual use of digitalis. In the present study the minimum level of proven use of digitalis was set rather high in order to minimize the risk of falsely positive classification. Moreover, because serum digitalis concentrations were measured only
in those who reported the use of it, this method certainly underestimated the prevalence. Even so, the method was very useful, because it provided an accurate minimum estimate of the prevalence of digitalis use in the population.

In ordinary clinical work serum digitalis concentrations measured in the absorption phase are practically meaningless. In this study, however, the measurements served basically two specific purposes. Firstly, to indicate the actual use of digitalis and secondly, to estimate the prevalence of patients with subtherapeutic serum digitalis concentrations. For the first purpose it makes no difference whether the measurements represent the absorption phase or the elimination phase. As regards the second purpose, the inclusion of absorption phase samples clearly tends to underestimate the prevalence of subtherapeutic serum digitalis concentrations.

The questionnaires were reviewed and the interviews carried out by specially trained personnel. The use of drugs (especially digitalis) was checked from appropriate documents and the recall periods were short and clearly demarcated. Furthermore, since digitalis therapy is part of well established medical tradition, the consumers are likely to know these drugs, at least by name. Under these conditions the questionnaires and the interviews can be considered fairly accurate. The repeatability of the questionnaire proved to be good. The variation was smallest between the health interview and the screening phase (Table 7). Most of this variation can probably be attributed to methodological factors, since the interviews were carried out by local public health nurses in the participant's home, whereas the completed questionnaires (in the screening phase) were reviewed with the participants by the mobile clinic nurses. Moreover, the interviews only inquired about use of drugs "at the moment" but all drugs used within the previous 3 months were recorded in the screening phase. The rest of the comparisons (Tables 8-10) were free from such methodological bias.

The extents of reported and proven use of digitalis were very close to each other. In the screening phase, 87% of the reported use could be confirmed by a significant serum glycoside concentration. This is a very high proportion, especially if one takes into account that 3.7% of the samples were missing or were drawn from patients taking proscillaridin A and, consequently, were not analysed at all. Moreover, because noncompliance with digitalis therapy is notoriously common (Johnston and McDevitt 1978), it was not even expected that the use might be proven in all those who reported it.
7.2. Results

The prevalence of digitalis use was slightly higher in women than in men. The difference was statistically significant (p<0.05), however, only for the reported use, not for the proven use (I). This might indicate that women are prescribed digitalis more frequently than men but on the average they use the drug less regularly. This view is further supported by the finding that sub-therapeutic serum digitalis concentrations were more common in women than in men (II, IV).

The prevalence of digitalis use observed in this study was much higher than that reported in the 1960s from a rural community in South-west Finland (Tuomi 1965). In that study the prevalence of digitalis use was less than 2 %. However, it should be noted that the study population of Tuomi (Tuomi 1965) was from the age group 41-60 and that the main aim of the study was not to investigate drug use but the prevalence of various heart diseases in the community. Relatively low prevalences have also been reported from other countries. For example, in the Swedish study by Bergman et al. (1976) digitalis users over 60 amounted to only 3 % of the population. In the UK, 6 % of those over 65 had been prescribed digoxin, the predominant glycoside (Tunstall-Pedoe 1978). In Gothenburg the prevalence was 14 % in 70-year-old people (Landahl et al. 1977). In Munich, however, the prevalence in the 30-69 year-old population was 7 %, a relatively high prevalence for that age group (Koenig et al. 1984). These findings are consistent with the drug sales statistics, which have shown that the Finnish sales figures are exceeded only by those of the Federal Republic of Germany (Friebel 1982).

In 1980 the annual sales of digitalis glycosides in Finland were 74 millions of DDD (Nordic Statistics on Medicines 1982a). This corresponded to about 200,000 DDD/day. Assuming the same number of digitalis users the prevalence in the Finnish population aged 30 years or over would be 7.6 %. There are at least two apparent explanations for the higher prevalences observed in this study. Firstly, the actual daily doses of digoxin, the predominant glycoside, are smaller than the DDD. The mean daily dose of digoxin was about 0.22 mg for men and 0.20 mg for women (III), whereas the DDD has been set at 0.25 mg (Nordic Statistics on Medicines 1982b). Secondly, the Finnish statistics do not include direct sales to hospitals (Nordic Statistics on Medicines 1982a). In Sweden about 7 % of the annual sales of digitalis have been direct sales to hospitals (Dahlström et al. 1978). On the other hand, the sales statistics include pediatric use of digitalis, which was omitted in this study.
The estimated number of digitalis users in this study (I) was clearly higher than that (200,000) calculated on the basis of the annual drug sales statistics (Nordic Statistics on Medicines 1982a). Even the lower 95% confidence limit of the number of those with definitely proven use of digitalis was 227,000. Interestingly, the number of digitalis users estimated on the basis of self-reported use of digitalis (about 300,000) was at least half the number that has been published in the UK (Hull and Mackintosh 1977, Tunstall-Pedoe 1978). The total population in the UK, however, is about ten times that of Finland.

Regional variation in the actual use of digitalis in Finland (I) has not been reported before. Comparable variation has been reported from Sweden and Czechoslovakia (Dahlström et al. 1978, Boman and Ögren 1981, Stika et al. 1979). These studies were based on regional drug sales statistics. Similar Finnish statistics are not available. However, the statistics of the Social Insurance Institution (Kokonaan korvattavien lääkkeisiin... 1981) have shown regional variation in the number (per 1000 inhabitants) of patients entitled to fully reimbursed drugs for heart failure. The observed regional variation in digitalis use could not be accounted for by different sex or age distributions between the social insurance regions. The variation might be partly explained by different patterns of cardiovascular morbidity. Another possible (and perhaps more likely) explanation is that the therapy is practised and controlled in different ways in the five regions (IV).

Although it is not possible to distinguish between real variation and methodological variation (repeatability), digitalis therapy seemed to be generally very consistent. The variation in reported use of digitalis increased with increasing interval between the questionnaires. The increased variation was very likely due to real changes in the medication. Most of the changes seemed to result from newly started therapies. In contrast, discontinuation of the therapy appeared to be rare. In addition to the 10 participants presented in Table 8, digitalis therapy had been started between the screening phase and the re-examination in 22 participants not belonging to the random subsample. On the other hand, all those who had taken digitalis at least within 7 days prior to the screening phase were still taking the drug at the time of the re-examination.

The proportion of digitalis users with sinus rhythm was very high (II). If we accept the proposition (Johnston and McDevitt 1979, Taggart and McDevitt 1980) that discontinuation of digitalis should be attempted in all these patients, about 9.4% of the Finnish population aged 30 years or over (246,000±21,000 patients) should undergo such a trial (Table 11). On the basis of previous experience (Hull and Mackintosh 1977, Fonrose et al. 1974, Johnston and
McDevitt 1979, Boman et al. 1981, Boman 1983a) at least half of these patients might be expected to do well without digitalis.

Even the number of patients with a stable cardiac state and a low serum digitalis concentration was rather high (Table 11). These patients are the most likely candidates for a successful discontinuation of digitalis (Boman 1983a, Johnston and McDevitt 1979, Liverpool Therapeutics Group 1978). Of course, some patients, in spite of a stable cardiac state, may need digitalis to prevent supraventricular tachyarrhythmias (Johnston and McDevitt 1979, Boman 1983a). Anyhow, the findings suggest that questionable use of digitalis is very common in Finland. The most obvious reason for this situation is the therapeutic tradition, according to which digitalis has largely been prescribed for the remainder of life. Under these circumstances digitalis prescriptions are likely to be renewed without considering whether the drug should be withdrawn or whether the dose should be changed. The externally poor control in half and the subtherapeutic serum digitalis concentration in about one third of the patients suggest that this indeed is what happens (IV).

Because of the potential risks of digitalis toxicity digitalis should not be used for questionable indications. The patients should therefore be evaluated periodically to decide whether digitalis is still indicated (Fonrose et al. 1974, Taggart and McDevitt 1980, Aronson 1981, Carlson et al. 1985). Since 90% of the patients seem to visit the attending doctor at least once annually, the basis for an effective patient evaluation ought to be good (IV).

The estimated prevalence of possible underuse of digitalis was low (II). The estimate was made on the assumption that all patients with atrial fibrillation should be treated with digitalis. However, digitalis is indicated only in those with a fast ventricular rate. The true prevalence of underuse of digitalis may therefore be even lower than that estimated.

Overall, the results indicate that the utilization of digitalis glycosides in Finland is often inappropriate. This is evident on the basis of the large number of patients in whom the therapy proved to be questionable or poorly controlled (II, IV). It would appear useful to create a consensus model for the treatment of heart failure and supraventricular tachyarrhythmias. The model should clearly state the role of digitalis glycosides in various clinical contexts. This might help to rationalize the utilization of these drugs.

The results of this study also stress the importance of developing new methods for continuous, systematic and comprehensive monitoring of drug utilization.
8. SUMMARY AND CONCLUSIONS

The utilization of digitalis glycosides was studied as part of the Mini-Finland Health Survey of the Social Insurance Institution. The survey was carried out in a population sample stratified to represent the Finnish population aged 30 or over. The sample size was 8000 persons (3637 men and 4363 women), 195 of whom were in long-term institutional care. Since the survey was met with a high response rate, the results can be generalized to the Finnish population aged 30 or over.

The methods comprised interviews and questionnaires asking about current and recent use of drugs. Detailed information on the use of digitalis and on the care of cardiovascular diseases was collected in supplementary interviews. The interviews were carried out by specially trained nurses who also reviewed the questionnaires and checked the reported drugs from prescriptions or package labels. If a digitalis glycoside was recorded, a blood sample was drawn for radiotinmunologic measurement of serum glycoside content. The methods also comprised standard chest X-rays and electrocardiograms for the assessment of cardiac state of the subjects.

The prevalence of digitalis use was found to be even higher than previously estimated on the basis of the national drug sales statistics. A significant serum glycoside concentration (>0.4 ng/ml for digoxin and lanatoside C, >6.0 ng/ml for digitoxin) proving the use of a cardiac glycoside was observed in about 9% of men and 10% of women aged 30 or over. On these measurements the minimum number of digitalis users in Finland was estimated at 248,000±21,000. The prevalence of reported use of digitalis was about 10% in men and 11% in women. On these grounds the number of digitalis users was estimated at 311,000±22,000. About 90% of all digitalis consumption was found to take place outside institutions.

The prevalence of digitalis use varied remarkably between the five social insurance regions. It was lowest in South-west Finland and highest in North Finland.

Digitalis use was found to be very stable. It appeared to vary in the course of time mainly due to newly started therapies, whereas discontinuation of the therapy seemed to be rare.

About 90% of digitalis users were in sinus rhythm. Sinus rhythm and normal roentgenographic heart volume was observed in half of all digitalis users. This was equal to about 4% of men and 5% of women aged 30 or over. On the basis of these observations the total number of digitalis users in stable cardiac state was estimated at
129,000±14,000. Since recent experience suggests that digitalis can be withdrawn without ill effect in at least half of such patients, questionable use of digitalis appears to be very common in Finland. On the other hand, underuse of digitalis was found to be rare.

More than 90% of the digitalis users were on digoxin, mostly administered as a single daily dose. Few patients were taking more than 250 µg per day. Serum digoxin concentrations were generally low and no toxicity was observed. Interindividual variation in serum digoxin concentrations was remarkable. On the other hand, intraindividual variation was small.

Few patients were taking digitalis as the sole prescribed drug. Among digitalis users the mean number of prescribed drugs was 4.2 for men and 4.6 for women. About 85% of all digitalis users generally consulted their "own" doctor. Although 90% of the patients receiving digitalis had consulted a doctor at least once within the previous 12 months, the control of the therapy was considered generally poor, since only half of the patients reported that they had made a further appointment. A subtherapeutic serum digitalis concentration indicating questionable and/or poorly controlled therapy was observed in about one third of the patients. The proportions of patients on poorly controlled, inadequate or questionable digitalis therapy varied remarkably between the social insurance regions.

In view of the large number of patients in whom digitalis therapy is inadequate, questionable or poorly controlled it seems mandatory to thoroughly reappraise the practice of prescribing this drug in Finland.
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