MEDICAL PRACTICE

Contemporary Themes

Clinical pharmacokinetics: a comprehensive system for therapeutic drug monitoring and prescribing

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Abstract

Clinical pharmacokinetics is an expanding scientific discipline which can make an impact on treatment in coronary care, intensive care, paediatrics, general medicine and surgery, and general practice. The aim of this study was to establish a rapid system of drug assay, to report the result, to assess the influence of pathological and clinical factors on the pharmacokinetics of certain drugs, and to use a computer to determine the optimum dosage of drugs. The clinical pharmacokinetics laboratory in Stobhill is available to all clinical departments and to general practitioners in the area. Digoxin, theophylline, and phenytoin have been assessed. Initial samples of these drugs showed that only about a third were in the therapeutic range; samples obtained after the issue of the laboratory report showed an improvement. The predictive performance of the computer program improved with feedback of one or two drug concentrations.

Dosages of drugs chosen on an empirical basis may not lead to optimum treatment, and by testing samples early the dosage of the drug can be adjusted. It is hoped that the results achieved will encourage other clinical, pharmaceutical, and scientific colleagues to develop laboratories along similar lines.

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Introduction

"Therapeutic drug monitoring" aims to promote optimum treatment by ensuring that plasma concentrations lie within a "therapeutic" range, above which toxicity occurs and below which the drug is ineffective.[1] Clinical pharmacokinetics embraces not only therapeutic drug monitoring but also an assessment of the clinical and pathological factors which modify the absorption, distribution, metabolism, and excretion of drugs in individual patients.

Many laboratories offer some form of monitoring of concentration of drugs, but special training and experience are needed to interpret these measurements. With these considerations in mind, we established a clinical pharmacokinetics laboratory three years ago in the department of materia medica with the help of a grant from the Scottish Home and Health Department. The specific aims were: (*a*) to establish a rapid and efficient system for drug assay; (*b*) to develop a clinically relevant reporting system; (*c*) to assess the influence of clinical and pathological factors on the pharmacokinetics of a number of drugs; and (*d*) to implement and further develop a computer approach to determine the dosage of drugs.

We present the results of introducing such a laboratory into clinical practice and describe the impact it has had on drug treatment.

Methods

DRUG ASSAY SYSTEM

Analyses of drugs were initially performed by homogeneous enzyme immunoassay (EMIT, Syva, Palo Alto) and radioimmunoassay (IMMO PHASE, Corning Medical). More recently, high performance liquid chromatography was introduced for economic reasons and for the analysis of larger batches of samples where speed was not important.

DRUGS ANALYSED

We considered that monitoring would enhance the safety and efficacy of treatment with digoxin, disopyramide, lignocaine, procainamide, theophylline, phenytoin, carbamazepine, phenobarbitone, and the aminoglycoside antibiotics.

DATA ACQUISITION AND REPORTING SYSTEM

A request card was designed to obtain essential information, including age, sex, height, weight, relevant biochemical findings, the full history of dosage, and the time that the sample was taken in relation to the previous dose. Any other pertinent information was obtained by pharmacists and medical staff.

A routine procedure was followed (fig 1). Firstly the plasma concentration was measured after an initial period of clinical observation. Secondly, the patient's pharmacokinetic state was assessed. This was relatively easy when the patient was on long term treatment—that is, at "steady state"—but more difficult in acute situations when a computer was required. Thirdly, a report was issued containing the result of the assay and advice on changes in dosage if these were indicated. A request for a further sample was also made to test the validity of any predictions made on the basis of the previous sample. This procedure was repeated if necessary.

INFLUENCE OF CLINICAL AND PATHOLOGICAL FACTORS ON PHARMACOKINETICS

Comprehensive clinical and pharmacokinetic information was collected routinely and stored on disk (PET microcomputer). Many of these data were subsequently analysed to determine which factors appreciably influence pharmacokinetics in selected groups of patients. These factors were then incorporated into interpretative computer programs used in the laboratory.

ESTIMATION OF PHARMACOKINETICS DURING ROUTINE MONITORING OF DRUG CONCENTRATIONS

A number of calculator and computer programs were available which helped the interpretation of routinely measured plasma concentrations. The most useful programs used one or two concentrations to provide an estimate of the way in which an individual patient eliminated a drug and this allowed selection of future doses which were most appropriate for that patient. This approach was first proposed in 1979[2,3] and 1980[4] and the data generated by the clinical pharmacokinetics laboratory were used to implement similar programs.[5,6] To test this approach in practice, sample concentrations at follow up from limited groups of patients in a variety of clinical circumstances were compared with those predicted by the program. Specifically, the profile of the plasma concentration over a period of 48-72 hours was first predicted on the basis of published nomograms. Concentrations were then measured three times in this period. The actual value of the third measurement (at 48-72 hours) was then compared with the value predicted using firstly the original nomogram, secondly, the first measurement, and then thirdly, the first and second measurements.

STATISTICAL ANALYSIS

Statistical comparison of observed and predicted values was made by calculating the prediction error (predicted—observed value) associated with each sample and then determining the mean (SD) prediction error.[7] The unpaired t test was used to show whether or not the mean prediction error differed significantly from zero. If it did, significant bias was present. Changes in precision were assessed by comparing standard deviations with the F ratio test.

Results

INFLUENCE OF REPORTING BY CLINICAL PHARMACOKINETICS LABORATORY

The clinical pharmacokinetics laboratory was available to all clinical departments in the hospital and to general practitioners in the region. On average, 330 requests for measurements of plasma concentrations were received every month, with a breakdown as follows: cardioactive drugs (digoxin, lignocaine, disopyramide, and, rarely, procainamide) 40%; theophylline, 18%; anticonvulsants (phenytoin, carbamazepine, valproic acid, phenobarbitone, and primidone) 27%; aminoglycoside antibiotics (gentamicin and occasionally tobramycin and netilmicin) 15%.

A detailed analysis of the measurements made on three drugs (figs 2-4) shows the impact of the laboratory on drug treatment. For this analysis, consecutive samples measured over a representative six month period were used, each sample being associated with a follow up sample.

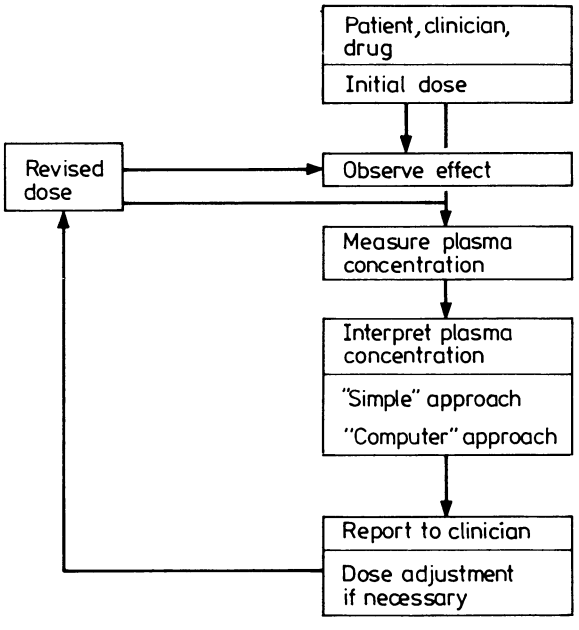

FIG 1—Flow chart of procedure routinely adopted in clinical pharmacokinetics laboratory.

Digoxin (fig 2; therapeutic range of 1·3-2·6 nmol/l (1·0-2·0 ng/ml))—Of 253 samples sent to the laboratory 88 (35%) were within the therapeutic range, 94 (37%) were above it, and 71 (28%) were below it. All patients with concentrations above 3·9 nmol/l (3·0 ng/ml) had digoxin toxicity. Samples obtained two to four weeks after the issue of a laboratory report had the following distribution: 167 (66%) were in the therapeutic range, 38 (15%) were "toxic," and 48 (19%) were "subtherapeutic." Half the patients with concentrations above 2·6 nmol/l (2·0 ng/ml) were still receiving up to twice the recommended daily dose, and a quarter of the patients with concentrations below 1·3 nmol/l (1·0 ng/ml) had not received the recommended increase in dose.

Theophylline (fig 3; therapeutic range 55·5-111 μmol/l (10·0-20·0 μg/ml))—Of 145 "initial" samples, 42 (29%) were within the therapeutic range, 16 (11%) were "toxic," and 87 (60%) were "subtherapeutic." All patients with concentrations above 166·5 μmol/l (30·0 μg/ml) had theophylline toxicity. Follow up samples showed the following distribution: 102 (70%) were in the therapeutic range, 7 (5%) were "toxic," and 36 (25%) were still "subtherapeutic" (about half of this group were still receiving doses less than those recommended by the laboratory).

Phenytoin (fig 4; therapeutic range 40-80 μmol/l (10·0-20·0 μg/ml))—Of 107 "initial" samples, 19 (18%) were in the therapeutic range,

15 (14%) were "toxic," and 73 (68%) were "subtherapeutic." Follow up samples obtained at outpatients after about four weeks had the following distribution: 48 (45%) were in the therapeutic range, 10 (9%) were "toxic," and 49 (46%) remained "subtherapeutic."

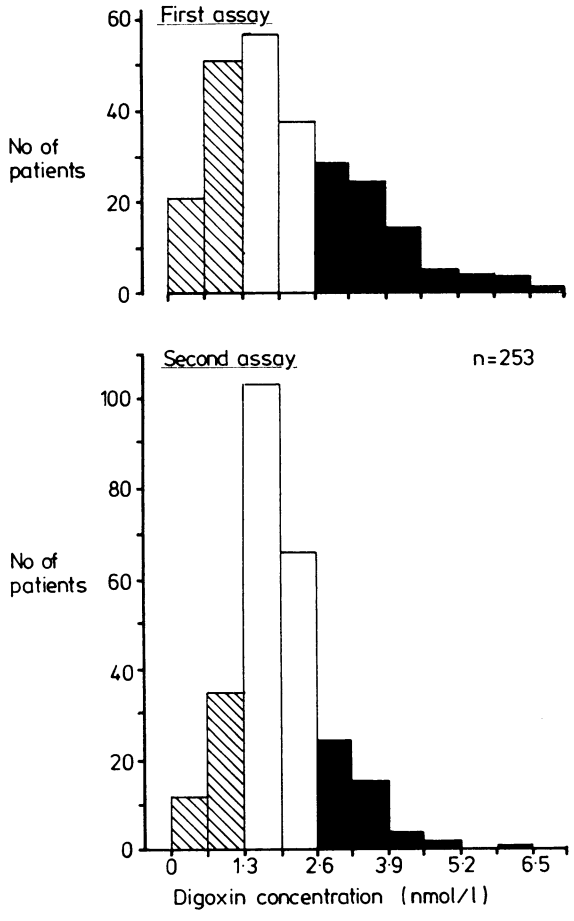

FIG 2—Distribution of digoxin concentrations relative to "therapeutic range" (1·3-2·6 μmol/l) before initial and after follow up advice.
Conversion: SI to traditional units—Digoxin: 1 nmol/l ≈ 0·78 ng/ml.
Lightly shaded areas represent "subtherapeutic" concentrations. Black areas represent "toxic" concentrations.

VALIDATION OF COMPUTER PROGRAM

The predictive performance of the computer program applied to digoxin, theophylline, and lignocaine was examined. The table shows the results.

In 18 patients taking digoxin, the mean prediction error using a nomogram alone[8] was 0·22 nmol/l (SD 0·82) (0·17 (SD 0·64) ng/ml). After the feedback of one concentration measurement it was 0·12 (SD 0·46) nmol/l (0·09 (SD 0·36) ng/ml), and after a second measurement, taken 12-24 hours later, it was −0·05 (SD 0·31) nmol/l (−0·04 (SD 0·24) ng/ml). These predictions were unbiased. Precision improved significantly ($p<0·02$) with feedback of one drug concentration but no further improvement occurred with a second concentration.

In 21 patients taking theophylline, the mean prediction error using a nomogram[9] was −15·24 (SD 43·61) μmol/l (−2·77 (SD 7·93) μg/ml). After one measurement it reduced to 1·43 (SD 20·85) μmol/l (0·26 (SD 3·79) μg/ml) and after a second measurement made within 12-24 hours it was 0·77 (SD 6·6) μmol/l (0·14 (SD 1·2) μg/ml). These predictions were unbiased. Precision, however, improved significantly as more information from measurements of concentration became available.

In 31 patients given lignocaine by infusion in the coronary care unit, the mean prediction error using a nomogram[10] was −6·09 (SD 6·21) μmol/l (−1·54 (SD 1·57) μg/ml). After one measurement made within 12 hours of admission, it was −2·29 (SD 5·82) μmol/l (−0·58 (SD 1·47) μg/ml) and after a second measurement, taken 12-24 hours later, it was −2·61 (SD 3·65) μmol/l (−0·6 (SD 0·99) μg/ml). These predictions were therefore consistently biased and the precision improved significantly ($p<0·02$) only when two concentrations were used.

Prediction analysis based on varying amounts of information

	Nomogram alone	+ First measurement	+ Second measurement
Errors of prediction (mean(SD))			
Digoxin (nmol/l) (n = 18)	0·22 (0·82)	0·12 (0·46)	−0·05 (0·31)
Theophylline (μmol/l) (n = 21)	−15·24 (43·61)	1·43 (20·85)	0·77 (6·6)
Lignocaine (μmol/l) (n = 31)	−6·09 (6·21)	−2·29 (5·82)	−2·61 (3·65)
Bias (p values)*			
Digoxin (nmol/l) (n = 18)	NS	NS	NS
Theophylline (μmol/l) (n = 21)	NS	NS	NS
Lignocaine (μmol/l) (n = 31)	<0·05	<0·05	<0·05
Precision (p values†)			
	Nomogram *v* first measurement	First measurement *v* second measurement	Nomogram *v* second measurement
Digoxin (nmol/l) (n = 18)	0·0167	NS	0·0167
Theophylline (μmol/l) (n = 21)	0·0167	0·0167	0·0167
Lignocaine (μmol/l) (n = 31)	NS	0·0167	0·0167

*Unpaired *t* test.
†F ratio test, significance adjusted for multiple (three) tests.
Conversion: SI to traditional units—Digoxin: 1 nmol/l ≈ 0·78 ng/ml; theophylline: 1 μmol/l ≈ 0·18 μg/ml; lignocaine: 1 μmol/l ≈ 0·25 μg/ml.

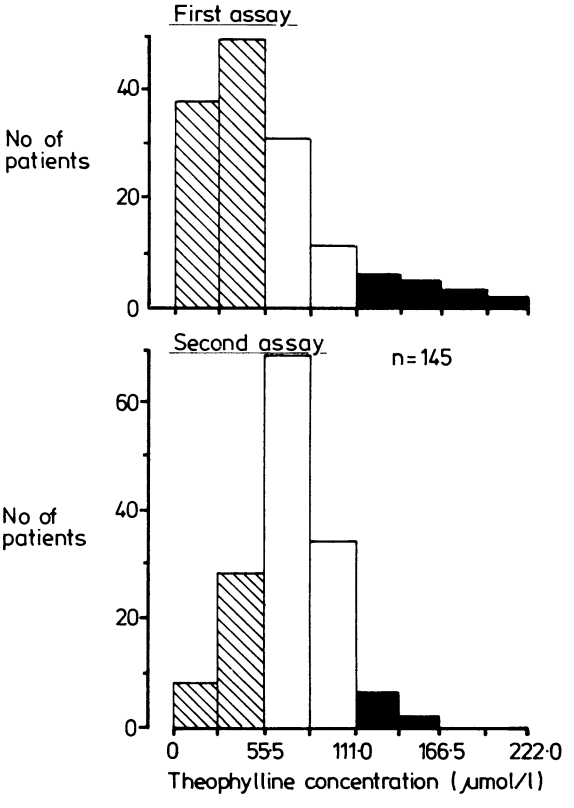

FIG 3—Distribution of theophylline concentrations relating to "therapeutic range" (55·5-111 μmol/l) before first assay and after second assay advice from the clinical pharmacokinetics laboratory.
Conversion: SI to traditional units—Theophylline: 1 μmol/l ≈ 0·18 μg/ml.

Discussion

The experience provided by the clinical pharmacokinetics laboratory has convinced us that this approach to therapeutic drug monitoring should be widely available. There is no doubt that dosage of drugs chosen on a relatively empirical basis may not lead to optimum treatment. A plasma concentration does not represent an observation that is superior to clinical observation or other relevant tests, but it provides an entirely objective view of one aspect of drug treatment. Without this

objectivity many patients may be deprived of optimum treatment, and many anomalies such as low grade toxicity, poor compliance, and drug interactions may be undetected. It also seems clear that many drugs will not be given a "fair chance" if alternative strategies are sought before it has been proved that acceptable ("therapeutic") concentrations are either ineffective or are associated with unacceptable side effects. In our experience a relatively low percentage of concentrations was initially in the therapeutic range with a significant proportion lying above or below it. These proportions improved dramatically after a report had been issued (fig 2-4). It must be emphasised, however, that while the adjustments in dose leading to the revised distributions were made principally on pharmacokinetic grounds, the scheme shown in fig 1 should always be followed, with similar emphasis on clinical (response to drug) and pharmacokinetic (drug concentration) observations. This

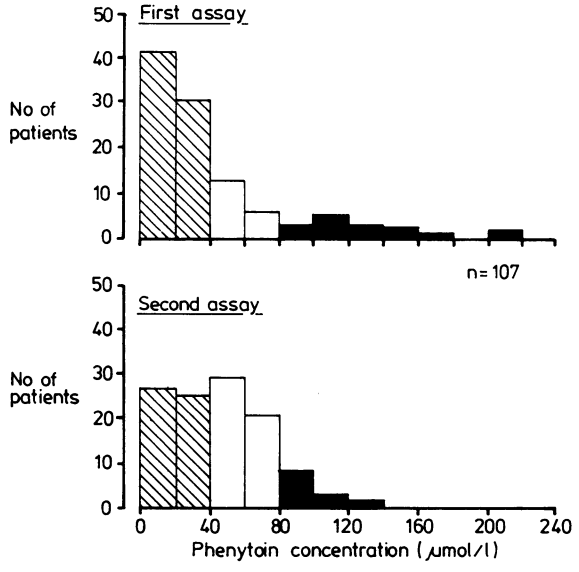

FIG 4—Distribution of phenytoin concentrations relative to "therapeutic range" (40-80 μmol/l) before final assay and after second assay advice from the clinical pharmacokinetics laboratory.

Conversion: SI units to traditional units—Phenytoin: 1 μmol/l ≈ 0·25 μg/ml.

implies close cooperation between staff in the laboratory and clinicians, and in our experience this was enhanced both by an active clinical pharmacology consultation service and by a pharmacy based drug information service.

The interpretative procedure, which is central to clinical pharmacokinetics, may be simple or complex depending on the drug, complexity of the history of the dosage, and the clinical circumstances. During long term treatment with many drugs a proportional adjustment in dosage may be all that is required. One or two drugs, however, such as phenytoin, require a slightly more sophisticated approach, using nomograms,[11-14] or calculator or computer programs. In acute clinical circumstances the simple approach will not be applicable and recourse should then be made to the type of feedback computer analysis we adopted. This feedback procedure uses Bayes's theorem, a statistical approach to the analysis of clinical pharmacokinetic data first proposed by Lewis B Sheiner.[2 3] A number of versions of this approach have now been developed[2-6 11 15] and fig 5 gives an example of the output from the program we used. The patient was a 61 year old man with a long history of chronic bronchitis. In spite of a relatively high dose of aminophylline (Phyllocontin, 450 mg three times daily) an initial subtherapeutic theophylline concentration was found, which indicated that 675 mg three times daily would be necessary to achieve satisfactory concentrations. That this increase in dose was appropriate was confirmed by a second analysis after two doses on the new regimen, and as an outpatient the concentration at follow up was 103 μmol/l (18·8 μg/ml) which confirmed that the predicted steady state level of 99 μmol/l (18·0 μg/ml) had been achieved.

In summary, we have found that clinical pharmacokinetics is welcomed and widely accepted by clinical colleagues in all major disciplines. Despite the fact that it deals with relatively few drugs, it has made an important contribution to treatment in such well defined disciplines as coronary care, intensive care, paediatrics, renal dialysis, general medicine and surgery, and general practice. In addition to having an important role

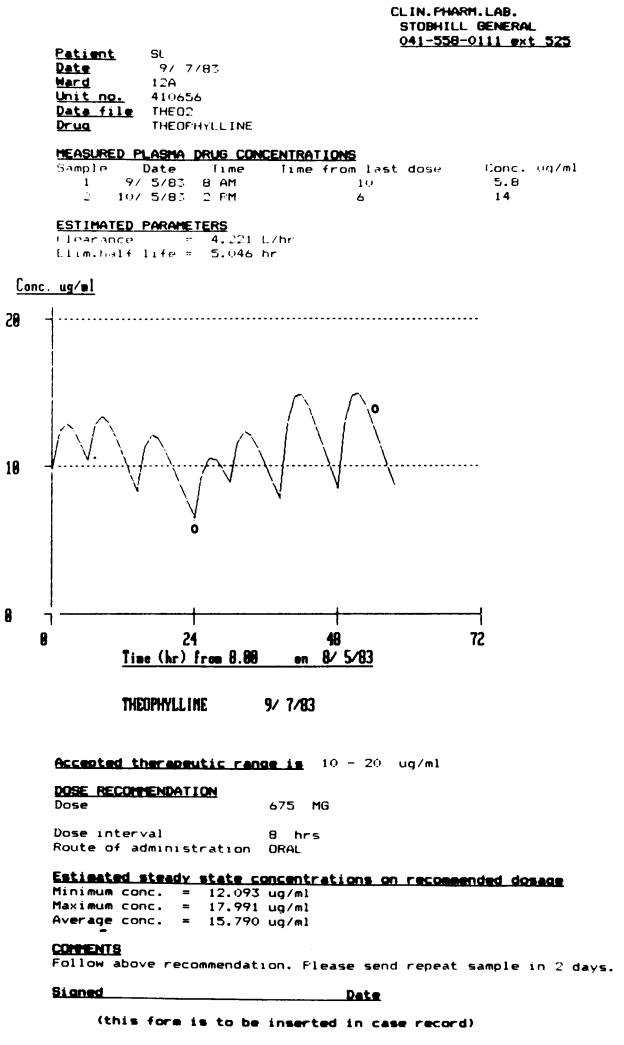

FIG 5—Example of computer report for permanent record in case sheet. Analysis and interpretation were based on two concentration measurements (0). Graph shows the estimated concentration—time profile relevant to dosage history, accurate details of which were available from 8 am on 8 May 1983.

in the teaching and understanding of therapeutics, it should conserve resources in the long run by bringing a useful degree of objectivity to one important aspect of drug treatment. Indeed, it may well be possible to extend the interpretative capacity of the statistical procedures outlined in this paper by including a consideration of response to drugs. The essence of this relatively new discipline is the ability to interpret plasma concentrations in a wholly clinical setting. This has been brought about by uniting clinical, pharmaceutical, and scientific skills, and it is hoped that this will provide a suitable model for others to follow.

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Clinical Topics

Tardive dyskinesia associated with metoclopramide

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Abstract

Eleven cases of tardive dyskinesia associated with metoclopramide have been reported to the Swedish Adverse Drug Reactions Advisory Committee from 1977 to 1981, 10 of which developed during the past three years. All patients were women, with a mean age of 76 years. Median duration of treatment before the onset of symptoms was 14 months. Calculated from total drug sales and prescription statistics the incidence of tardive dyskinesia during treatment with metoclopramide was estimated to be one in 2000-2800 treatment years. Extrapolation of data on long term treatment (more than six months) of patients aged 70 years or more, from a survey based on individual prescriptions yielded an incidence of more than one in a 1000 patients.

Long term treatment with metoclopramide is accompanied by a substantial risk of developing tardive dyskinesia especially among elderly people.

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Introduction

Metoclopramide stimulates peristalsis of the oesophagus and the intestine and accelerates gastric emptying.[1] It also has the ability to block central dopaminergic receptors.[1] Because of these properties metoclopramide has been used in gastroenterology and as an antiemetic. Neurological side effects such as acute dystonia may occur at the start of treatment,[1] and reversible Parkinsonism later. The first report of a more serious long term complication, tardive dyskinesia, was published in 1978 in this journal,[2] and was soon followed by more cases.[3] An analysis of reports to the Swedish Adverse Drug Reactions Advisory Committee in relation to data on sales and prescriptions during the past years indicate that this serious complication of treatment with metoclopramide may well be more frequent than hitherto recognised.

Methods and materials

Voluntary reporting of suspected adverse drug reactions to the Swedish Adverse Drug Reactions Advisory Committee started in 1965, and since 1975 the reporting of fatal, otherwise serious, and new reactions are compulsory. The reports are scrutinised by a medical officer and discussed by a working party, and the probability of a causal relation is finally settled by the full committee, which has representatives from many clinical specialties. Since 1972 total drug sales, expressed as value, volume, or so called defined daily doses[4]—have been provided by the National Corporation of Swedish Pharmacies. Since 1974 this corporation has also run a continuous prescription survey where the patient's age and sex, and the name, amount, and dosage of the drug are recorded from a random one in 288 sample of all prescriptions dispensed from the pharmacies.[5] Individual drug purchases are provided from the county of Jämtland, where all purchases have been recorded for a random one seventh of the population since 1970.[6]