Attitudes to development of drug therapy in Scandinavia

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Development of drug therapy includes the following elements: the introduction of better drugs on the market, the broad application of clinical pharmacological principles in drug utilization and an increased rationality among doctors and patients towards drug therapy. The ultimate goal must be that medical needs, and morbidity in particular, will determine the extent of drug use. The development of new drugs is one of the most important aspects of the development of drug therapy, particularly when new pharmacological principles are introduced into clinical medicine. However, new essential drugs are not infrequently being prescribed on wrong indications and in the wrong dosage by physicians or they may not even be ingested by the patients who need them. Recent epidemiological studies suggest that there are marked geographical differences in the prescription of common drugs both between and within countries (Sjöqvist & Agerås, 1984). There are also marked differences between physicians in their prescribing pattern for common diseases. Unfortunately none of these studies has been able to find rational explanations such as geographical differences in morbidity or as a Norwegian epidemiologist put it 'huge differences and small explanations' (Hjort *et al.*, 1984). Recent research suggests that prescribing rationality is a physician characteristic related to his age, training and patterns of obtaining drug information (Haayer *et al.*, 1982). It is therefore naive to believe that rational drug therapy can develop without paying attention to the many factors, rational and irrational, that determine the quality of drug prescription.

The introduction on the market of drugs for which there are no obvious medical needs, represented by the plethora of 'me too' drugs, does not usually contribute to the development of rational drug therapy. Sometimes it may have the opposite effect by causing confusion among health professionals and patients and by diluting the efforts of academic institutions and health authorities to arrange relevant continued education of doctors in clinical pharmacology and therapeutics.

The attitudes to the development of new drug therapies may well be different in the Scandinavian countries than in other parts of the world. A look at the drug scene reveals that, for example, in 1974 the number of registered drugs was much smaller in Norway, Denmark and Sweden than in some other European countries (Figure 1). On a number of occasions Scandinavian doctors and health authorities alike have shown less enthusiasm about the introduction of new drug therapies than their colleagues in the international medical community. Let us name a few.

Fixed combination drugs are less common on the Scandinavian drug market than elsewhere in Europe. This may be the result of the recognition of the fundamental clinical pharmacological principle of practising an individualized dosage schedule of each component at a time (Reidenberg, 1974). An increasing number of doctors are interested in keeping an appropriate balance between non-pharmacological and pharmacological methods of treating their patients, the most prominent example being the balance between psychotherapy and drug therapy in mild depression and psychoneurosis. A number of leading internists in our country have declared that they do not see a need for drugs in the treatment of overweight since the effects of presently available drugs are shortlasting and dietary restrictions ought to be the treatment of choice. And even a first class innovation such as cimetidine was met with considerable scepticism among important opinion-makers on the Swedish drug scene because the marketing people did not sharply distinguish between its documented and approved use in ulcer therapy and its possible use in treating vague symptoms of gastritis (Rosell, 1978). The Norwegians were even more reluctant to accept this new drug (Lunde, 1984).

An important initial step in developing rational attitudes to drug therapy among the medical profession was the establishment of hospital drug formulary committees consisting of clinicians, pharmacists and M.D.-pharmacologists. This was done in the beginning of the sixties with the aim to improve drug selection and to keep the

Figure 1 Registered drug products in Scandinavia and some other European countries in 1974.

hospital drug bill within reasonable limits. The intellectual and economical success of the first few committees at the university hospitals resulted in the formation of such committees in all major hospitals in Sweden and a subsequent demand for more consultants in clinical pharmacology. A similar development has taken place in the other Scandinavian countries.

The committees of the larger hospitals annually issue a booklet containing the drugs recommended for the catchment area and essential facts about them. These drugs amount to about 10% of the available drugs on the Swedish market, presently about 200–300 drug products. There are three selection criteria: the overall pharmaceutical, pharmacological and clinical documentation, therapeutic tradition and price—in that order. On the basis of all these factors the committee makes a preliminary recommendation of drugs to be used for a specific disease and this recommendation is then subjected to review by various specialists in pharmacotherapy and adapted according to the local needs. During the reviewing process there are several possibilities to initiate discussions and seminars in drug evaluation. A final recommendation is then issued. In many respects the working principles of the Nordic drug committees can be considered as a prelude of the WHO essential drug concept (WHO, 1977).

Special measures had to be taken to assess the therapeutic tradition in quantitative terms by developing methods for recording drug utilization. As an example, figures for drug use expressed in so called defined daily doses (DDD) are now available in Norway and Sweden. A DDD is the average maintenance dose of the drug on its major indication and if chosen correctly the DDD/1000 inhabitants should come close to the morbidity (Bergman & Sjöqvist, 1984). This monitoring system has a great potential for follow-up studies of doctors' attitudes to drug therapy and to specific drugs. Figure 2 shows an example with oral anticoagulants, where Norwegian and Swedish doctors had different attitudes to drug selection. In the early seventies the dominating drug in Norway was warfarin (80%) and dicoumarol had less than 10% of the market while the opposite was true in Sweden. In the choice between these two drugs a strong case can be made for warfarin on pharmacokinetic grounds because dicoumarol preparations may be erratically absorbed and because dicoumarol has concentration dependent kinetics in contradistinction to warfarin (Breckenridge, 1977).

A national drug committee within the Department of Drugs of the Swedish Medical Board of Health and Welfare continuously issues recommendations regarding drug usage. These elaborate review articles are written by experts in the

Figure 2 Wholesale figures between 1972 and 1980 of oral anticoagulants (●, warfarin, ▼ dicoumarol, ■ phenindone) in Norway and Sweden expressed in per cent of total defined daily doses/1000 inhabitants. In mid-1973 an expert committee suggested that warfarin might be the drug of choice among oral anticoagulants. Subsequently there was a drastic change of Swedish doctors' attitudes to this class of drugs and their prescribing habits came close to those of their Norwegian colleagues.

various fields of pharmacotherapy and are distributed free of charge to all physicians and pharmacists in Norway and Sweden. In mid-1973 the Norwegian authors who were asked to write the issue on anticoagulants suggested that warfarin should be used as the first line oral drug (Lunde & Stormorken, 1973). This recommendation was supported by many of the Swedish hospital drug committees and slowly a new pattern of drug selection developed at the national level (Figure 2). In the beginning of the eighties warfarin dominated the Swedish market. No doubt the manufacturer of warfarin was happy to join the movement. However, the important aspect of this example of therapeutic auditing is the demonstration that it seems to be perfectly possible to influence the prescribing pattern of the medical profession within a relatively short time period using straight intellectual arguments. The necessary prerequisite is of course that there is an infrastructure for effectively disseminating new knowledge to the prescribers.

The Scandinavian drug committee system has hitherto had little influence on drug usage in primary health care (PHC) which accounts for up to 80% of all drug prescriptions. Measures are now taken to increase the collaboration between hospitals and PHC in questions related to drugs. This is important for a variety of reasons: (i) the bulk of drug utilization occurs in PHC; (ii) in spite of this, clinical drug evaluation is usually performed in selected hospitalized groups of patients who may not at all be representative of the population at large that ultimately will be treated with the drugs; and (iii) the reporting of adverse drug reactions from PHC is by no means

Figure 3 The county of Jämtland in mid-Sweden (black region in the small national map) can be utilized for epidemiological studies of drug utilization. The county has only one general hospital in the city of Östersund and its drug committee has fruitful collaboration with primary health care. A random sample of 17 000 individuals identified by date of birth (13% of the population) has had their drug prescriptions monitored since 1970. In one part of the county (hatched area) plasma samples may be obtained for studies of drug compliance in a subsample of the monitored population.

Figure 4 Cumulative first prescriptions of atenolol to outpatients in the county of Jämtland, distributed according to prescribing physician category. R = date of registration of atenolol in Sweden.

proportional to the degree of drug prescribing in this field.

High priority must therefore be given to research on factors that determine the attitudes of PHC-physicians to drug therapy. The county of Jämtland study (Figure 3) in which the prescriptions to 17 000 inhabitants have been monitored since 1970 (Boethius & Wiman, 1977) has pro-

vided some interesting new data on attitudes to drug therapy in PHC. A striking finding has been that newly marketed drugs break through quicker in PHC than in hospitals, exemplified with atenolol (Figure 4) and naproxen (Figure 5). By contrast chest physicians were as quick as general practitioners to start prescribing a theophylline product with improved biopharmaceutical properties (Figure 6). A second feature of drug attitudes in PHC is the pattern of discontinuous treatment of chronic disorders (Boethius, 1976) such as hypertension (Figure 7) and a third is the proportion of drop-outs among patients who have been prescribed new drugs or drugs for chronic use.

Follow up studies are now being performed in order to describe the ultimate fate of drugs in PHC. The method is illustrated with nifedipine (Adalat®), registered in February 1980 for the treatment of angina pectoris. The first 40 patients on the drug in the county of Jämtland were followed up in August 1983 (Ugander & Boethius, to be published). Thirty-one patients had stopped medication—one did not even start taking the drug (Figure 8). Two stopped because of improved condition and five because of lack of

Figure 5 Cumulative first prescriptions of naproxen (Naprosyn®) to outpatients in the county of Jämtland distributed according to prescribing physician category. R = date of registration of naproxen in Sweden.

Figure 6 Cumulative first prescriptions of theophylline in a new pharmaceutical preparation (Theo-Dur®) to outpatients in the county of Jämtland distributed according to prescribing physician category. R = date of registration of the drug product in Sweden.

effects. Three patients died and twenty patients stated that side effects caused the discontinuation, in half of the cases within the first week. In all, twenty-two patients had only one prescription

filled. Of the nine patients who still were on the drug at the follow-up seven took the drug regularly and two took it sporadically. By relating the number of side effects reported to the Adverse Drug Reaction Committee to drug utilization an index of 6.8 side effects per DDD $\times 10^6$ could be calculated for the nation as a whole. The index for the county based on this follow-up would be much higher.

Another follow-up concerned prazosin (Peripress®) marketed in November 1978 for use in hypertension. Five of the first 20 women who were prescribed the drug developed urinary incontinence during treatment. In no case did the patient herself, nor her doctor connect the symptoms with the drug intake although this side-effect has a rational explanation at the α -adrenoceptor level. All women became continent following cessation of treatment.

These examples suggest that essential information on how drugs are accepted in PHC by

Figure 7 Pattern of antihypertensive drug treatment in a patient between 1970 and 1978. The beginning of each line indicates the time of dispensation, the length of line signifies the period of time that the dispensed quantity should last. Note that the patient is without medication for considerable periods of time.

Figure 8 Follow-up of the first 40 patients in the county of Jämtland with prescriptions of nifedipine (Adalat®). See text for explanation.

prescribers and patients may be obtained from prescription monitoring in a defined population. Needless to say such studies must be done using appropriate controls such as standard therapy. The simplicity of the approach and its relevance for the real world of drug prescribing are particularly attractive features.

The county of Jämtland study can also be used to examine doctors' attitudes to the application of clinical-pharmacological principles in drug utilization such as individualization of drug dosage schedules (Boethius & Sjöqvist, 1978). Some years ago we reported here in Dundee in a symposium on Drugs in the Elderly that there was no apparent reduction in the elderly of doses of drugs being excreted unchanged such as digoxin in spite of the decreased renal clearance of such drugs in these age-groups (Sjöqvist, *et al.*, 1979). Seven years later a significant drop in the mean digoxin doses prescribed in the elderly had occurred (Table 1). This tendency is also seen in a nationwide prescription survey in Sweden. Possibly, this is the result of a therapeutic audit initiated in Jämtland. The continuous introduction of modern clinical-pharmacological principles in drug utilization in primary health care will be important for the development of rational pharmacotherapy.

While the development of new drugs is vitally important for rational drug therapy other aspects of pharmacotherapeutic research must also be emphasized. Pharmacokinetic and drug metabolic studies of old drugs have since long been advocated as a potential source of deriving better

Table 1 Prescribed mean daily dose (mg) of digoxin in 1975 and in 1982 in the county of Jämtland, Sweden

Age group	1975 (n = 1585)	1982 (n = 1664)
15-59	0.23	0.23
60-69	0.22	0.22
70-79	0.22	0.19
80-	0.20	0.16

therapy. This research strategy may very well experience a renaissance, not the least in the light of the many pitfalls during preclinical and clinical testing of new chemical entities. Examples of drug metabolites of potential interest in this regard from our own research include carbamazepine epoxide and 10-OH-nortriptyline. The former has been shown to have significant analgesic effects in patients with trigeminal neuralgia (Tomson & Bertilsson, 1984). The hydroxylated metabolite of nortriptyline has similar potency as the parent drug in inhibiting noradrenaline uptake but has very weak binding to cholinergic receptors compared to nortriptyline posing the provocative question whether this compound might be useful in depression and more easy to tolerate by the patients (Wagner *et al.*, 1984). It is of particular interest that the major E-10-hydroxylated isomer has these promising properties and we are now in the process of evaluating its kinetics and metabolism in man.

Figure 9 Frequency distribution of dosage intervals of pilocarpine eye drops during the first and second (dotted line) 20 day periods. Before the second period the patients underwent a 30 min drug education and tailoring program. The patients were not aware of the recordings but were informed before the monitor records were used. From Norell (1979).

Rational drug therapy ultimately requires the full cooperation of our patients. Modern technology permits objective observations of patients' medication behaviour. By utilizing a medication monitor Norell (1979) in our hospital has demonstrated a high frequency of irrational compliance with prescribed drug regimen (Figure 9). The encouraging aspect is however that the medication behaviour can be improved by relatively simple educational programmes.

Inappropriate drug use by physicians and patients may account for 10–15% of hospital admissions to departments of medicine in Scandinavia (Bergman & Wiholm, 1981). It is of considerable interest to note that several studies in Sweden indicate that overdose and inadequate therapy are equally important in causing hospital admissions. The remedies for these problems include not only increased patient education but also increased follow-up of patients and increased pharmacotherapeutic training of health professionals.

It is becoming increasingly obvious to health professionals, health administrators and politicians in Sweden that the development of drug therapy towards higher quality will require novel ways of collaboration between the parties involved. The increased involvement of the public

health sector in drug information programmes and studies of the 'kinetics' of drugs in the society is now followed by an increased interest in applied drug research. Negotiations between the pharmaceutical industry, public health authorities and medical schools have led to a number of improvements of clinical trials, and not least clarified the role of the clinical investigator *vis à vis* his employers, colleagues and patients. A national committee has suggested a number of changes in the existing regulations of clinical trials with the important aims to increase their quality and to decrease unjustified suspicions from laymen about this kind of research. The government is also actively stimulating collaboration between industry, academic departments and hospitals in the various facets of drug research. Special interest is being paid to developing epidemiological methods for longterm follow-up of patients. It is slowly being appreciated that only the test of time will decide whether a new drug regimen represents a useful advance in therapy.

The original work discussed or presented in this paper was supported by grants from the Swedish Medical Research Council (03902) (FS) and the Swedish National Corporation of Pharmacies (GB).

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