DRUG UTILIZATION STUDIES AND DRUG MONITORING IN THE NETHERLANDS

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Summary. - Drug utilization research is a research area of increasing importance, as well in the Netherlands as elsewhere. In this article an overview is given of the situation in the Netherlands. Three types of studies are distinguished: descriptive studies, studies of the determinants of drug use and studies of the impact of drug use. Descriptive studies are needed to understand the present situation and to detect problems. If these problems are to be solved it is important to understand the factors that determine drug use. By looking what the impact is, the value of drug use for health care can be assessed. It is also an important tool for developing systems for drug monitoring at a patient level. At present community pharmacists play an important role in drug monitoring at the patient level. A problem still awaiting a solution is how to implement such systems effectively.

KEY WORDS: drug utilization studies, drug monitoring, drug databases.

Introduction

Drug utilization and drug monitoring are lively discussed issues today in society. Drug monitoring can be described as: keeping an eye on actual drug use, to pinpoint problems and suggest corrections. As such it is closely related to drug utilization studies, that also look into actual drug use. Drug utilization studies moreover provide the building stones for the construction of drug monitoring systems on a patient level. In this article an overview will be given of the situation in the Netherlands concerning these building stones - drug utilization studies - before turning to the issue of drug monitoring.

Drug utilization studies

In the last decade attention for drug utilization studies increased strongly in the Netherlands. In 1979 a few isolated projects existed; at present the issue is integrated in the research programmes of 5 universities at a number of public health agencies. The field has further been formalized since the establishment of a section for drug utilization studies and pharmaco-epidemiology within the newly founded Dutch Society of Pharmaceutical Sciences. The increased attention has not come out of the blue. A number of factors can be pointed out, that make this development understandable. In the first place drug use has become an important tool in the cost containment policies of the health authorities. If such policies are to be effective it is important to know how drugs are being used in order to pinpoint problem areas and to evaluate the measures taken [1, 2]. The second major factor is the changing role of the pharmacist in the drug use process. Instead of only dispensing, the pharmacist is now becoming increasingly active by monitoring drug use and providing information services for both prescriber and the
general public. Also here drug utilization data have an important role. Finally, society does not tolerate any risk when taking drugs. Detection of these risks is needed when the drugs are actually on the market, i.e. postmarketing surveillance studies. Moreover early warning signals for groups at risk should be developed; again requiring information of actual drug utilization patterns.

Now what does all this increased attention mean in terms of actual research? Basically three types of studies can be distinguished:
- descriptive studies;
- studies of determinants of drug utilization;
- studies of the impact of drug use.

In this article we describe the types of studies undertaken in the Netherlands of which examples are given. The databases concerning drug utilization available will be discussed.

Descriptive studies

Descriptive studies serve to profile the present situation and pinpoint problems. Different aspects may be stressed when looking into drug utilization statistics (Table 1). An important field is the drug utilization by specific high risk groups in the population. In this area studies are being done analysing drug use of pregnant women [3], the elderly [4-7] and children. Another kind of descriptive study focusses on utilization of specific drug groups. Thus benzodiazepine use, for example changes in its pattern over time, is being investigated, an issue which has received continuously attention over the years. Although many initiatives have been developed to decrease its use, the problem is still there. Other ongoing studies in this category concern antibiotic use in hospitals [8], irrational drug choice in hospitals, long acting hormone preparations in the western world in comparison to the developing world [9, 10] and the use of diuretics as antihypertensives for women.

Drug costs demand attention primarily because of their relevance for the health authorities and insurers. Recently a new method has been developed to analyse trends in drug expenditure [11]. The method can be used to distinguish between three different components contributing to a change in drug expenditure for a specific class of drugs. The first component is the "norm" change, an overall change in volume due, for example, to changes in the morbidity pattern. The second component refers to changes in prescribing behaviour, for example in drug choice. The last component is the change in price. When applied to antihypertensives, the method showed that the total increase in expenditure in this group was mainly due to a shift in prescribing behaviour from the already existing drugs to the recently introduced ACE-inhibitors. Secondly an overall increase in prices contributed to the change. The overall volume decreased slightly resulting in a negative contribution of this component. In contrast, an overall increase in volume was the second factor explaining the increase in expenditure for drugs for peptic disorders, after a change in product choice, while the prices contributed only slightly to the change in this drug group. The use of this method may thus increase the transparency of the market. It shows the policymaker where and how interventions should take place.

Interdoctor variation is the subject of another type of descriptive study. Here the issue is to find information about prescribing behaviour of physicians. At present the issue is studied within specific therapeutic areas, in relation to other therapies and in relation to the indication. A last type of descriptive study is being undertaken in the Netherlands are anthropological studies, using the "bottom up" method to understand drug use, i.e. small groups of people are extensively studied using a qualitative approach. An example of this type of research is a study on drugs and children in Europe, in which the Netherlands were involved. Another example concerns the treatment of diarrhoea, cough and fever in the Philippines [12-14].

Determinants of drug utilization

Drug utilization is in part determined by the availability of products, but also by the knowledge and attitudes of the health professionals and the general public (Table 2). Availability of products reflects both official regulation and health insurance schemes. Studies in this field comprise an ongoing analysis of economic measures and their repercussions in Europe [1] and the feasibility of integrated drug policies. One of the problems that face the policymakers is that a measure may be profitable in one field but have undesired effects in another. For example, to lower reimbursement for drugs might lead to an increased demand for other types of therapy, that are less appropriate or more expensive. If a more integrated approach would be possible, such problems may be prevented.

A central issue in the other determinant of drug utilization, knowledge and attitudes, is how these determine actual drug use. Understanding of these aspects is essential for all efforts to promote rational prescribing and drug use. Thus, a study of the drug choice process of the general practitioner revealed the importance of the direct professional environment, besides knowledge about the charac-

<table>
<thead>
<tr>
<th>Table 1. - Descriptive studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug utilization of high risk groups in the population</td>
</tr>
<tr>
<td>Drug utilization of specific drug groups</td>
</tr>
<tr>
<td>(Trends) in drug expenditure</td>
</tr>
<tr>
<td>Interdoctor variation</td>
</tr>
<tr>
<td>Drug utilization in small patient groups (anthropology)</td>
</tr>
</tbody>
</table>

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<tr>
<th>Table 2. - Determinants of drug utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug policy</td>
</tr>
<tr>
<td>Drug information</td>
</tr>
<tr>
<td>education of physicians</td>
</tr>
<tr>
<td>education of patients</td>
</tr>
<tr>
<td>the role of the pharmacist in drug information</td>
</tr>
</tbody>
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characteristics of a drug [15, 16]. A new project investigates the
drug choice process in the hospital. Impact of written
versus verbal information on prescribing was analysed
with special reference to the impact of the Dutch drug
bulletin [16, 17]. It showed that highly valued written
material, as the drug bulletin, can have an impact on
knowledge, on the perceived utility of a drug and on
prescribing. Verbal information, transferred in a face to
face encounter, seems to be slightly more effective. Phar-
maco-therapeutic committees, where the local pharmacist
meets regularly with the surrounding general practitio-
ners, are one way in which information can be successfully
transmitted verbally [18, 19]. In the Netherlands approxi-
mately 25% of the general practitioners are involved in
such committees [20]. Another approach is the use of an area
clinical pharmacologist, someone who is trained in med-
cine as well as in pharmacology and drug therapy. Such an
area clinical pharmacologist can support existing pharma-
co-therapeutic committees, reach out to those general prac-
titioners not yet involved and form more in general a
bridge between pharmacy and medicine on a regional
instead of a local level. This approach is in an experi-
mental stage [21].

The evaluation of (written) information for patients is
the second major field of interest in this area. One study,
looking at a WHO brochure about drugs and the menopau-
se, revealed the importance of knowing the beliefs and
attitudes of the target group, which may be in conflict with
the professional view [22, 23]. If information is to have an
impact it should incorporate these beliefs of the target
group. A shortcoming of the brochure mentioned was that
it represented too much the professional point of view,
neglecting the ideas of the women about the menopause.
Thus, for example, no attention was paid to “getting fat” as
possibly related to the menopause, a concern mentioned
often by the women interviewed. It also showed that an
increase in knowledge (in this case, about osteoporosis as
related to the menopause) may increase anxiety, an unde-
sired effect of the brochure. A new development for patient
education is the use of patient specific information leaflets
in the pharmacy, providing only directly relevant informa-
tion about the drug(s) dispensed for a specific patient. The
first experience with this form of information shows a
general appreciation, but more attention could be paid to
individual instructions for use [24]. More in general,
pharmacy and drug information is an important area of
research, their role in information to physicians (as men-
tioned above with regard to the pharmaco-therapeutic
committees) and to the general public. Since a large
majority of the Dutch pharmacies are computerized (ap-
prox. 90%) feedback on prescribing of the individual
physician is possible, an important tool for continuously
promoting rational prescribing.

Impact of drug use

Inappropriate drug use can lead to failure of treatment,
to avoidable injury and to a waste of resources. Moreover,
as mentioned before, society does not tolerate risks in the
use of drugs. Adverse effects are therefore an important
issue in the field of drug utilization studies (Table 3). One
type of study focusses on the detection of adverse effects
using postmarketing surveillance. An interesting method
here is the so-called prescription sequence analysis. This
approach uses pharmacy based prescription drug histories
to detect adverse effects. Basically, drug use is used as a
tracer of possible adverse effects. The method is based on
the assumption that a temporal sequence between the
prescribing of two drugs may indicate an adverse reaction
to the first drug, i.e. that the second drug is used to treat an
adverse effect of the first drug. The method is particularly
valuable for substantiating spontaneous case reports. Thus
it was possible to show that the alleged link between the
use of flurazepam and the occurrence of depression was
probably not a causal one. In this case antidepressives were
used as the tracer drug [25]. An important limitation of this
method is that only drugs with a single well defined
indication can be used as tracers of adverse effects.

The use of pharmacy based prescription drug histories
is also being developed for detection of the population at
risk. The complete drug history can be used as an indicator
of risk by looking at the concomitant or sequential use of
other drugs, to changes in dosage schemes and to switch-
ing patterns within one drug group. These features can
then be used as signals for specific action [26]. Finally, by
combining the information from pharmacy records with
information from other health related databases, signals of
possible adverse effects can be detected. Using this ap-
proach further evidence was provided for a possible asso-
ciation between ovulation induction (by clomiphene) and
neural tube defects [27].

Yet another type of work being done in the field of drug
use and its adverse effects is the compilation of works of
reference. First to be mentioned here is Meyler’s Side
Effects of Drugs with its accompanying annual Side Ef-
ects of Drugs Annual [28, 29]. More recently an interna-
tional study was added in collaboration with the USA,
investigating the legal aspects of drug induced injury [30].
The chronic use of drugs is increasing. It is therefore
important to know what the effects of such use are. At
present a pilot study is going on developing criteria for
valid indicators of chronic drug use based on pharmacy
records and evaluating different methods of data collect-
ion [31]. The impact of drug use is not limited to adverse
effects; drug use may have a much broader effect on the
quality of life of the patient. This type of study is under-
taken with regard to the use of antiepileptics [32].

Table 3. - Impact of drug use

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<th>Adverse effects</th>
<th>Detectors of adverse effects</th>
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<td>Detection of population at risk</td>
<td>Reference works</td>
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Drug use and quality of life
Databases

There are a number of databases of drug utilization in the Netherlands, each of which has advantages and disadvantages.

Health fund data. - The drug utilization data available from this source are detailed. They include information about the kind of drugs prescribed, the amount of every drug (defined daily doses can be calculated) and the costs per drug. All this can be differentiated for individual physicians and pharmacists. The major disadvantages are that these data are limited to outpatient prescribing. Moreover the health funds cover only 60% of the population. Since coverage depends on income - all employed who earn less than a defined level - the population covered is not representative for the total population. Health funds are organized on a regional level, drug utilization data are therefore collected on a regional level. Until 1984 these were aggregated on a national level. Since then no national database exists. However, a new database is being developed, based on a national representative sample.

Pharmacy records. - As mentioned before, approximately 90% of Dutch pharmacies are computerized. The possibilities of these records for drug utilization are now being explored and exploited, examples of which are provided above. The records contain the same information as the health fund data, but the drug related data are linked to patient characteristics as well, such as age and gender, allowing the development of individual drug histories. Besides that, an important asset of these records is that they cover health fund patients as well as privately insured patients. Health fund patients are necessarily registered at one pharmacy, so that their data are complete. Of private patients this is not ensured, although probably most patients go to the pharmacist closest by. Disadvantage is, first of all, that by their very nature these data are only available at a local level. However, a database has been set up based on the records in 100 pharmacies all over the country [26]. Since in the rural areas, drug dispensing is still often confined to the general practitioners, pharmacy based data are not representative for this part of the population. However, dispensing facilities in these general practices are increasingly computerized.

Hospital pharmacy records. - Drug utilization data available within a hospital setting consist of the kinds of drugs used and the amount per drug. The pharmacy based data are limited to dispensing records, implying they cannot be differentiated per physician. Differentiation at the patient level is possible using patient records. However, these are usually not computerized nor accessible for review purposes. Drug utilization studies at the patient level are therefore in practice extremely time consuming and almost impossible. At present, little information exists on drug utilization within the hospital at a national level. The data that are collected, are only within one hospital.

Institute of Medical Statistics (IMS). - This institute collects data on a commercial base in close cooperation with the pharmaceutical industry. It has information on the complete turnover of every drug in terms of volume and in terms of money on a national level, in the Netherlands as well as in other countries. A major disadvantage is the use of the concept of "counting unit" as the measure of volume. This unit refers to the smallest available counting unit, such as tablets. The advantage is the international character of these data and the fact that they are available for a large number of years. Besides these turnover figures, IMS collects diagnosis related data. Every three months 325 physicians provide 7 days of complete registration of every patient contact. Data include information on patient characteristics (age and gender, etc.) and on the diagnosis.

Records of a national study of general practice by the Dutch Institute of Primary Health Care (NIVEL). - This study collected data about all the different events occurring during 3 months in 1986/1987 in a representative sample of 160 general practitioners. Data collected include, among other things, the reason for encounter of the patient, the diagnosis of the physician, the therapy provided (medicinal or other), several patient characteristics, etc. In case of drug therapy, the kind of drug and the amount prescribed are noted. This study enables an in-depth analysis of drug use in general practice.

Drug monitoring

The question now is how these data can and are being used for drug monitoring. Descriptive studies are important for policy makers: to identify problem areas and also to monitor and evaluate policy measures taken. For monitoring at a patient level the results of these studies can point to priorities. Knowledge about the determinants of drug use helps the communication process when actually monitoring drug use of specific patients. Knowledge of the impact is needed to decide what we should maintain.

Before going on it is important to delineate more clearly the concept of drug monitoring: many different interpretations seem to exist and a number of closely related terms are being used when dealing with quality assurance (Table 4).

Table 4. - Definitions of concepts of quality assurance

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<tr>
<th>Drug level control</th>
<th>Dose control by measurement of drug plasma level</th>
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</thead>
<tbody>
<tr>
<td>Drug monitoring</td>
<td>Medication Surveillance, i.e. control of prescriptions (dose, interactions, contraindications, compliance etc.) on a patient level</td>
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<tr>
<td>Drug use review</td>
<td>Current use evaluated against agreed standards</td>
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<td>Medical audit</td>
<td>Discussion of diagnosis and treatment of individual patients</td>
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If we now turn to see what elements drug monitoring on a patient level consists of, we can distinguish 5 elements:  
- dose control;  
- drug choice control;  
- interaction control;  
- contraindications;  
- compliance.

It becomes immediately clear that the pharmacist or the dispensing physician is central in this drug monitoring process. In Europe pharmacists consider drug monitoring a major task, as was found when the views of key persons in community and hospital pharmacy in 12 European countries were investigated. However the actual situation is different: in only one country drug monitoring is in fact realised as a task of the retail pharmacist, while in two countries this is partly the case. The same situations apply to hospitals [33].

In the Netherlands the ideals are partly realised: ca. 80% community pharmacists are involved in computer-based drug monitoring. One reason for the the problems of realising these services on a community base put forward by pharmacists concerns the perceived antagonism from physicians. A study in the Netherlands looked into this problem and found the situation to be different (Table 5) [19].

General practitioners (GPs) consider medication surveillance by pharmacists a much needed instrument, particularly with regard to patients with a high risk for drug induced injury. GPs see this need much more than the pharmacists thought.

How is such drug monitoring at a patient level operating?

It is based on the patient medication history, stored in the pharmacist’s computer. In this computer are also patient data (age and gender) and a number of warning signals in the software as well as a code for the prescriber. The most extensive system (used by 300 pharmacists) has stored 96 clinically important interactions and 23 clinically important contraindications out of the myriad of possible interactions and contraindications. This is a very important feature for the practical applicability of the system. If all possible interactions and contraindications would be used everybody would drown in all the details. There are also warning signals for compliance - when a prescription is offered for refilling within the period it was meant for - indicating overuse or - if a prescription is offered when too much time has passed - indicating undertuse.

Little is known of the effect of such drug monitoring systems for actual drug use. A pilot study was therefore started to look at what happens when a computer signals an interaction. Two such signals were studied: the use of non-selective betablockers by diabetics and the use of betablockers alongside the chronic use of indomethacin. The combination of non-selective betablockers and antidiabetics should be prevented because non-selective betablocking agents may lower the blood sugar level; moreover they may mask the symptoms of hypoglycaemia. The warning against concomitant chronic use of indomethacine and the use of betablockers is included because indomethacin may reduce the effect of the betablocker and a good alternative is available (sulindac).  

Two approaches were used to look into the effect of warning signals issued by the computer. First of all the frequency of use of the described combinations was investigated in five community pharmacies. Diabetics and chronic users of indomethacin (> 3 prescriptions) were identified in the period June 1988 - June 1989. Medication histories were collected by pharmacy students of the University of Groningen with portable computers and analysed at the University. Secondly the management strategy of the pharmacists was investigated by registration of the responses of the pharmacist in the 5 participating pharmacies to every warning for these possible interactions during 3 months (June-September 1989).

In this period 787 diabetics were identified, of whom 384 used at the same time antihypertensives: 164 of the latter used betablocking agents (selective and non-selective as well as combinations with betablockers). Non-selective betablockers were used by 31 diabetics. This means that 8% of all diabetics who used an antihypertensive were using a combination that may show an undesirable interaction. Chronic indomethacin users also keep on using betablockers, despite warning signals, while no sulindac (the alternative for indomethacin for these patients) was found. Of the 137 chronic indomethacin users, 65 used an antihypertensive, of whom 14 (22%) a betablocker.

These results indicate that computer issued warnings are not enough to extinguish the use of undesirable combinations. To get an indication why this may be the case, the reactions to computer signals were registered during 3 months. Concerning the warning signals in this study 53 were registered, of which only 4 (less than 10%) resulted in action of the pharmacist in the direction of the prescriber.

Table 5. - The need for drug monitoring by community pharmacists as perceived by pharmacists, general practitioners and pharmacists’ expectations of what general practitioners think

| Medication Surveillance (% needed) |
|-------------------------------|-----------|
|                               | All patients | High risk groups |
| Pharmacists                    | 20         | 63            |
| General practitioners (GP)     | 30         | 62            |
| Pharmacists expectations of GP’s opinions | 12    | 30            |

Source [19].

From this pilot study we can learn that:
- interactions signalled in computerized drug monitoring systems do not necessarily lead to better prescribing;
- one reason for this lack of effect may be a lack of feed back to the prescribing physician.

The latter point is related to what was mentioned before in regard to the determinants of drug use. Understanding of these determinants may help the communication process. This aspect, adequate communication between pharmacists and physicians, seems at present to be the weak link when considering drug monitoring.

Conclusions

The importance of drug utilization studies and the related issue of drug monitoring at the patient level is at present well recognized in the Netherlands. Much effort is put into trying to understand what is happening now and how the drug use process can be optimized. The introduction of the computer has greatly increased the potential for this. At present drug monitoring at the patient level occurs mainly by community pharmacists. Shortly computerized patient management system will also be used in the surgery of the GP which can support the decision making more directly. Hospital are also in the process of developing adequate systems for drug monitoring. The first experiences, however, point to the fact that, important at the computer may be as a tool, the challenge now is the integration of its use in the everyday health care process. For this aspect a better understanding of the determinants of the drug is needed.

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