METHODS FOR THE DETECTION AND STUDY OF UNWANTED DRUG EFFECTS

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Ensuring the quality of services

By 1990, all Member States should have built effective mechanisms for ensuring quality of patient care within their health care systems.

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METHODS FOR THE DETECTION AND STUDY OF UNWANTED DRUG EFFECTS

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Note

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Introduction

A WHO Symposium on Methods for the Detection and Study of Unwanted Drug Effects was held in Kiel, Germany, from 26 to 29 November 1990. The meeting was organized jointly by the WHO Regional Office for Europe and the WHO collaborating centre for public health research in Kiel; it was made possible by the generous financial support of the Federal Ministry for Youth, Family Affairs, Women and Health. Professor Fritz Beske was elected Chairperson and Professor David Lawson, Vice-Chairperson. The Co-Rapporteurs were Dr Reindhardt Hanpft and Dr Win Castle.

In the course of a decade, many meetings and seminars have been held on the problems of adverse drug reactions (ADRs). Many methods have been presented, theories advanced, and various forms of experience analysed. In such a field, much of the methodology is necessarily experimental and subject to constant modification. For those who are not experts on these topics it can sometimes be difficult to determine what constitutes established knowledge, which methods are still only emergent, and which techniques have been left behind by progress.

The present meeting set out to review the current state of the art at the beginning of the 1990s. It considered systematically the various methods that have been designed and employed; it examined restrospectively experience on adverse effects in a number of specific therapeutic fields and looked at potential problems in currently active and expanding fields; and it examined the progress made in a number of individual countries in developing satisfactory means of ensuring that drugs are as safe as they can be, and identifying and quantifying those risks that are unavoidable.

The present report on the meeting is intended as a guide to the many health professionals, authorities and corporations engaged in this field. In particular, it is hoped that those concerned with the public policy implications of safe health care will find this overview of the current situation helpful.

Spontaneous reporting systems

The move to spontaneous adverse reaction reporting systems, which is almost unique to the field of pharmaceuticals, developed in the late 1960s as a reaction to the thalidomide disaster. Experience in some countries thus extends over nearly a generation, and the merits of the method can be considered well established. The same applies to the problems likely to be encountered; because of these problems, the resultant databases are often much smaller, less consistent and of lesser clinical quality than some would wish.

Structure

The role of the physician

The experienced physician, and in particular the general practitioner, is at the heart of any such system; its growth and limitations will always depend on the extent to which he or she is encouraged to participate, as well as on the role accorded to drug safety in medical education, both undergraduate and postgraduate. Doctors will be likely to report only if they know that their notifications are taken seriously, are handled promptly, confidentially and authoritatively, and are properly acknowledged, and if requests for supplementary information and testing reach them at once. Physicians will be most likely to respond if the demands made on them are reasonable and the forms and other procedures (such as computer links in both directions) are simple.

It must constantly be emphasized that notifications to a reporting system relate only to observations of "suspected" adverse effects. Attempts to impose any form of obligation on a physician to report seem pointless, since the most vital input into such a system consists only of early suspicions in the mind of an observant physician. Nor has the principle of paying the physician to report been accepted.

The principle of confidentiality

The principle of confidentiality is fundamental; the physician's trust in the centre to which the report is made must be such that there is no hesitation in being entirely open with facts and suspicions, knowing that no other party will be informed about the identity of the original case without the agreement of the parties involved, and that the information will never be used as a basis for disciplinary or other action against the reporting physician. Trust in such a system necessarily grows slowly and only where it is deserved; attempts to establish new systems and regulations sometimes overlook this point.

Though some form of identifier and some personal data may be needed to avoid double registration of a single incident and in order to identify risk groups, the closed nature of the individual doctor/patient relationship must not be breached. Where the medical staff of the pharmaceutical company concerned require additional information from the practitioner, it may for this reason be advisable for them to request it through the monitoring agency; the reverse may also be true. The confidentiality issue as regards the individual patient clearly must not (and need not) mean that an emergent drug problem is hidden from the profession or the community.

The role of the monitoring centre

The physician will sometimes feel the need for information and advice on an adverse reaction issue on which he or she has reported. The monitoring centre should be capable of providing information (such as a summary of the background literature or an outline of similar earlier reports) and interpretation. Whether the centre can do more will depend on its nature. Those monitoring centres that are also government agencies may be unable to accept reponsibility for advising the physician as to how he or she should act, for example in treating a given adverse reaction or deciding for or against continuation of treatment. Agencies that have been accorded a greater independence may be freer to assist the physician, but on such issues the clinical pharmacologist may be a more appropriate consultant, and it is regretted that clinical pharmacology has developed but slowly in many countries.

Limitations on monitoring systems and centres can be both financial and organizational. The staff of a monitoring centre must be accorded sufficient status and finance to do its work to an adequate standard. It should, for example, be possible to use an advisory council as well as experts attached to the centre, and on individual matters there must be the means to consult specialists, to invite reporting physicians for consultations, and to involve industry where necessary. Where problems of finance arise it can be relevant to calculate the total cost to the community of adverse reactions and to estimate the (probably substantial) extent to which these can be reduced by an adequate monitoring and information system. In view of the apparently favourable cost-benefit ratio and the advantages of good monitoring, it is fair to expect the costs of adverse reaction monitoring systems to be shared, for example between the taxpayer, the health insurance system and the pharmaceutical industry.

The role of the pharmaceutical industry

The industrial role in this field will only mature fully with the development within companies of independent medical units for adverse reaction monitoring, free of commercial motives or pressures. There is an encouraging trend in this direction, particularly in some larger companies. Increased emphasis and focus on the mechanisms of various adverse reactions particularly by companies, could help predict and identify other adverse reactions earlier.

The role of the World Health Organization

The WHO International Drug Monitoring Programme began in 1968 as a pilot project to collect and process reports of suspected adverse drug reactions. A Drug Monitoring Centre was established in Geneva in 1971 and moved to a collaborating centre in Uppsala, Sweden, in 1978. The database currently comprises some 800 000 reports of suspected adverse drug reactions.

In the course of 22 years it has experimentally used many techniques to determine the limits within which the data collected from national monitoring centres can be used as a totality. The fact that the standards and completeness of reporting have varied between countries (and over time within countries) clearly renders it impossible to treat the data as if the database were entirely homogenous. Its value in early signal generation and in determining where unusual events can be dismissed as coincidental or should be followed up (because parallels are to be found elsewhere in the system) is considerable.

Two recent developments - the appointment of a senior medical director and the decision to open up the system for wider use - are reasons for encouragement; the time appears to have arrived at which rapid further

development in the quality and usefulness of the system (and of the use actually being made of it) can be anticipated. The problems that remain are primarily still those of the variable quality of input from Member States and of the limited staff capacity in many of these national centres and at Uppsala.

It is clear that the central role of the WHO centre is that of a database, a data distribution post, and a resource for developing better methods for using adverse reaction information. The interpretation of signals and subsequent action naturally remain within the domain of the regulatory authorities and industry.

The current opening up of the WHO system to broader use is attractive to the pharmaceutical industry. The industry has long taken the view that, rather than being obliged to supply each national regulatory authority with "foreign" reports of suspected adverse reactions, it would be better to supply reports in a standardized format to one centralized database. The CIOMS[a] initiative was taken with this in view and has been successful. However, if the WHO database can assume this role it should be encouraged and assisted to do so. It was to be hoped that data could be exchanged electronically in both directions between companies and the central database, but it must also be passed from WHO to the national regulatory authorities concerned in a timely manner. If this can be done, all legal obligations could be met and a great deal of investment and work saved. This would also render it unnecessary to consider the establishment of another international centre elsewhere.

There is now good reason for the WHO centre to evolve as rapidly and effectively as possible, not only so that its role can be developed but so that its place

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[a] Council for International Organizations of Medical Sciences.

as a repository of national monitoring data can be consolidated, the quality of the data held improved, and experiments in its use actively continued.

Operation of the WHO centre could benefit from the experience of all the parties using it, and a broader advisory group could include the adverse reaction monitoring experts of the pharmaceutical industry. Extra resources for the centre will be needed if it is to perform these roles, and it is to be hoped that WHO will give high priority to securing extrabudgetary funding. With the widening of the circle of users a new pool of financial supporters may become available.

Methods

Nature of data sought

In principle, spontaneous monitoring systems exist to accelerate recognition of entirely unexpected drug reactions. It is important to look not only for associations of a drug with particular individual signs and symptoms but also for drug-associated clusters, occurring together or successively. These will commonly be groups of known symptoms but in an unusual association. Such emergent "syndromes" or clusters should be expertly assessed by clinicians in order to identify possible groups of adverse effects having a common etiological basis. It may also be necessary to look for associations between a cluster and a particular dose level or mode of use. Conscientious initial manual screening by clinicians of all the adverse events recorded for any single patient may provide hints as to possible clusters, which can then be methodically searched for in large databases. Facilities for follow-up are especially important in relation to these cases of possible new syndromes.

Analysis of cause-effect relationships

In determining whether an "event" may be drug induced or not, some elements are clearly more influential in the analysis than others. Experienced investigators will tend to apply many of these criteria instinctively, but it can be helpful to draw up check-lists, irrespective of whether they are used in a more sophisticated manner in the form of algorithms.

There are many different types of algorithm that can be used to test the drug/event assocation using these factors. Some are complex, and certain algorithms (e.g. Bardi and Adrian) are mathematical.

By and large, algorithms are sometimes helpful but involve disproportionate effort if used routinely. The terms in which their outcomes are expressed may themselves be liable to variable interpretation. Good analysis of the individual case report by experienced clinicians remains all important.

Other methods of surveillance

General principles

Use of complementary methods

There remains a need for complementary methods of adverse reaction monitoring other than spontaneous reporting. It is clear that pre-marketing and post-marketing studies complement one another, as do spontaneous reporting systems and specific prospective investigations.

There is every reason to develop automated, high quality, multipurpose data resources in Europe to provide the basis for future observational studies of drug

safety. Standardization of how textual data is handled is a prerequisite. With the increasing computerization of medical care in various countries, such integration of resources should be feasible and would represent a better use of the available means than merely investing in one individual study or system after another.

Studies in different populations

There are a number of instances in which much of the pre-marketing work was undertaken in a specific geographical area where population characteristics may be substantially different to those in other parts of the world. While there is a move to accept, for regulatory purposes, clinical data obtained in other parts of the world, the question as to whether different populations might not react in a different manner will often still need to be answered definitively. This presents a new challenge to post-marketing surveillance.

Cost-benefit considerations

The more ambitious approaches to the study of adverse reactions can involve very heavy investment. Where this work is clearly needed in the interests of public safety, the expenses involved may have repercussions on the cost of providing health care.

Changes in dosage

It is clear that where doses are substantially modified after a drug has been marketed, this may render irrelevant much of the pre-marketing work, at least as far as type A adverse reactions are concerned. The problem is not always avoidable, but where such changes in the dosage level or pattern are introduced, specific supplementary studies of adverse reactions are likely to be called for.

The study of ADRs in controlled clinical trials

Controlled clinical trials are well suited to the testing of hypotheses concerning both desired and possible undesired effects of a pharmaceutical product. In such a trial it is important to ensure that all adverse events are recorded, the question of their possible causal relationship to the treatment arising only during the analysis phase. It is important that a watch be kept for entirely unexpected possible adverse events and not only for those that might be anticipated and are listed in the protocol. Serious suspected reactions noted during the pre-marketing studies must be reported promptly to the authorities and to the ethical or other supervisory committee. Formal statistical analysis should be used to determine whether or not an adverse event has occurred significantly more often on the treatment group than on the control group.

The limitations of controlled clinical trials prior to marketing, as regards the detection and quantification of adverse reactions are:

- the unavoidably limited size and duration of even the largest studies as compared with exposure to the drug after marketing;

- the fact that after marketing the drug may reach various hitherto unidentified risk groups not represented during controlled studies; and

- the fact that co-medication and hence interactions are less likely to be present during controlled studies than later.

The chance of detecting reactions can be increased if:

- one examines carefully the reasons for drop-outs and deaths that may reflect serious or poorly tolerated adverse effects;

- efforts are made to correlate adverse events with patient characteristics, events observed and animal studies and with co-medication before concluding that they can be set aside;

- the formulation used and the mode of manufacture are identical to those of the product actually to be marketed;

- the pharmacology (including immunology, dynamics and kinetics) of the drug is carefully considered before a trial begins, so that the list of anticipated possible effects is as wide as it can reasonably be.

The study of ADRs in cohort and case-control studies

Cohort studies

These provide an opportunity to study multiple outcomes, and to investigate infrequently used drugs; there is relatively little bias in the initial exposure information, though care has to be taken to distinguish it from outcome data. It is important to have good details of entry characteristics. Long-term studies are expensive, and the methods are often the subject of controversy. There are also problems to overcome in maintaining the integrity of the cohort and in avoiding the appearance of a promotional element, questions of data audit, and problems of patient confidentiality. Many such studies have, however, stood the test of time. The existence of an earlier established cohort can be particularly useful in times of crisis when a serious challenge to the safety of a drug arises, e.g. from

spontaneous reporting schemes. Cohort studies initiated soon after marketing are of particular value in examining safety in previously unevaluated situations, such as the use of the drug in pregnancy or the elderly.

Case-control studies

The conclusions from such studies are more often challenged due to difficulties in agreeing on suitable control groups. In fact, case-control studies can be highly effective in hypothesis testing. The need for a control group could be debated. As the majority of drug disasters in the past have been due to rare serious adverse effects involving the skin, the neurological and haematological systems, the kidneys and liver, the use of networks or disease registers focusing on these target areas deserves consideration.

Monitored release

The idea that it will sometimes be advisable to release a drug onto the market only on certain conditions, rather than unconditionally accepting or rejecting it, is logical and is today widely accepted. The most important condition is likely to be that certain supplementary work be undertaken to complete the view of the drug's risk and safety.

Of the various approaches developed, that of obligatory monitoring of adverse reactions in a wide range of patients (and in some cases all individuals for whom a new drug is prescribed) subsequent to release is likely to be most successful; increasing possibilities to do this are offered by the ever wider computerization of medical practice and records. Coordinated monitoring of a drug in several or all countries of the European Community is becoming feasible, particularly with new measures that may result in virtually simultaneous approval in more than one member country. Such monitored

release is likely to be most useful where a drug is expected to be used long term by a large population.

While the associated registration may for a time be regarded only as "provisional", the requirement for monitored release should not be taken by the physician or the patient as inferring that prescribing the drug is thought to involve particular risk. The patient should, however, be informed of the fact that treatment will be part of a such a complementary study.

It seems logical for the company that developed the drug to coordinate this work, but it may in part be entrusted to independent consulting firms. Such companies will be well advised to establish independent bodies of advisers to support them and to ensure the proper handling of sensitive and confidential data.

The duration and extent of such specific monitoring will necessarily vary, depending on the nature of the drug and its use. It has been suggested that a cohort of at least 10 000 patients is needed. It may take a considerable period (a year or more for some drugs) to recruit this number, and even with a group of this size the patients involved may prove not to be typical of those likely to need and use the new product in the long term. Follow-up of these patients may need to be prolonged to detect late effects such as cancer, particularly in those situations where it is not possible to identify a cohort that can be monitored long term using automated, multipurpose databases. The findings should always be published.

Patients who receive a new drug in an existing class of compounds will commonly be those who have shown poor earlier tolerance. They may therefore represent a group that is particularly prone to develop adverse effects, and early monitoring may for this reason give an excessively negative picture of the new drug's safety.

Whereas it is normal for a physician who carries out a clinical trial for a corporation to receive reimbursement for time and expenses, the question of reimbursement for participation in monitored release is disputed. The aim is to obtain neutral unbiased reporting, so it is important that the method of financing will not interfere with these aims. It would seem that where (as is the case in most countries) physicians are adequately reimbursed by the community for patient care and treatment, their participation in the monitoring process can be regarded as a normal part of the process of care and does not justify special reimbursement. Certainly no large payment should be made such as might influence the physician's attitudes or prescribing; sometimes a small reinbursement for expenses may be justified.

The quadripartite Post-Marketing Surveillance (PMS) guidelines published in the United Kingdom have much to commend them and are being updated. Something similar may be adopted by other countries, taking into account the different organization of medical care.

Record linkage

Taken alongside other techniques, record linkage systems provide a useful input into adverse reaction monitoring. Record linkage may identify new useful effects of drugs as well as adverse reactions, and may indicate in which situations a drug is most effective.

Where medical records are to be used in record linkage systems they must meet certain standards. They should be capable not only of testing hypotheses but also of generating hypotheses, and this is dependent on "events" rather than "reactions" being recorded. They must register exactly not only the nature of the services provided (drug, dose, intake) but also temporal data. The data must be longitudinal and not just relational; experience with pioneer record linkage systems indeed

underlines the need for longitudinal data over long periods. The drug used must be precisely specified, as details of its pharmaceutical composition and manufacture may be relevant. The diagnosis must be specified according to an agreed coding system.

Adverse events (irrespective of whether they are considered drug-related or not) must similarly be coded methodically; for this purpose the ICD-9 (International Classification of Diseases) can be used. For the sake of consistency, it seems preferable to use the same coding system for both diagnoses and reactions rather than classify the latter according to one of the specific classifications of adverse reactions currently available.

In this as in some other fields of adverse reaction study, one must maintain confidentiality as regards the identity and history of the individual patient. But this is not a barrier to using details from individual records if identifiers are correctly chosen.

Drug utilization data, available in sufficient detail to indicate both the size and the characteristics of the population and the subpopulations exposed to the drug, must be complemented as far as possible by drug information from other sources. The need for data on national drug usage can be exploited to develop national drug safety record linkage systems. These relational databases may need to be used with some caution; however, the breakdown into a very large number of subgroups may involve much more effort than the results justify.

Observational studies in a single centre

A large hospital, with a monopoly on care in its own area and reliable local drug utilization data, can check for any excess occurrence of a given pathological condition in patients using a particular drug, as compared with others in its class or with the population

at large. Observations collected in this way can usefully complement other forms of research into adverse reaction incidence.

The strategy will involve:

- a systematic review of selected diagnoses applying strict clinical criteria;
- use of a structured questionnaire;
- applying a causality algorithm;
- correlating the number of cases with sales figures that were geographically and time specific.

The merits of such an approach can include the lack of notification bias such as occurs in spontaneous reporting systems, the possibility of applying consistent clinical criteria for inclusion, and the availability of reliable information on changes in reported reactions over time. Naturally, if the study is not population based one will not be able to obtain data on absolute risks or test hypotheses, but only a ranking order of the studied drugs. And if disease distribution and/or drug use is highly heterogeneous, the data obtained can be misleading.

For this and certain other types of quantitative study reliable drug utilization data are of great value. Data obtained from public health sources can usefully be complemented by those collected by market research agencies, and it is to be regretted that the latter are not commonly made available outside industry.

Consensus points

1. The aim of improving adverse reaction monitoring systems is to accelerate the identification of serious reactions and the situations in which they occur, so that

as few patients as possible will suffer unnecessarily. No system is likely to be perfect and some serious reactions will always be detected much later than one would wish.

2. In order to deal with rare associations, one must at present rely on spontaneous reporting systems augmented by the establishment of disease registers designed to record data on target-organ systems commonly involved in drug-related toxicity. Whenever possible, individual patients noted by these systems should be investigated in detail.

3. In order to deal with more common associations of adverse events with drug therapy, new resources need to be developed as a matter of urgency. The preferred facilities would comprise several complementary multipurpose databases. These resources should be established to coincide with the proposed completion of the "single market" of the European Community in 1993. The multipurpose database would include:

(a) facilities for studying drug exposure in general practice, in pregnancy, at the extremes of life, and longitudinally in individuals over substantial periods;

(b) facilities to systematically record all admissions to hospital (with discharge diagnoses), all deaths (classified according to local certification procedures), and any major life-threatening events not included in the above definition;

(c) facilities to assess basic medical records so that these can be verified and relevant data extrated;

(d) facilities for recording anonymous individual patient information at the point of data processing.

These multipurpose databases should permit efficient record linkage; they must therefore offer the chance for a balanced appraisal of the numerator, by insuring that a denominator and relevant demographic data are wherever possible available.

3. The World Health Organization's Adverse Reaction Monitoring Programme at Uppsala has reached a point at which it has very great potential for contributing to knowledge in this field. It is vital that it now be further developed with extrabudgetary funding, rather than that other similar systems be established elsewhere.

Annex 1

LIST OF WORKING PAPERS[a]

Summaries

ICP/DSE 166/6	Monitoring of adverse drug reactions (ADR) in patients in mental hospitals: results from the AMUP Project 1979-1989, by B. Müller-Oerlinghausen and L.G. Schmidt
ICP/DSE 166/7	Scope and limitations of causality assessment, by Dr W.M. Castle
ICP/DSE 166/8 Rev.1	Discovery of adverse drug reactions: debate on the paradox of clioquinol and SMON, by Dr Justus Gelzer
ICP/DSE 166/9	Uses and limitations of a global reporting pool, by Ms M. Lindquist
ICP/DSE 166/10 Rev.1	Monitoring of selected drugs by office-based physicians, by R. Hanpft, M. Hannig, E. Becker and F. Beske

[a] Copies are available from the Pharmaceuticals unit, WHO Regional Office for Europe, 8 Scherfigsvej, DK-2100 Copenhagen O.

ICP/DSE 166/11	Methods of detecting and quantitating unwanted drug effects. Cohort and case-control studies, by Dr D.H. Lawson
ICP/DSE 166/12 Rev.1	The record linkage system: a duality of purpose, by M. Lee Morse
ICP/DSE 166/13	Where can the numerators and denominators be sought to quantify risks?, by Xavier Carné, M.D. and Joan-Ramon Laporte
ICP/DSE 166/14	Promoting and developing spontaneous reporting systems, by Dr E. Napke
ICP/DSE 166/15 Rev.1	The long-term safety of antihyperlipidemic drugs, by J. Findlay Walker
ICP/DSE 166/16	Monitored release, by Dr Ronald Mann
ICP/DSE 166/17	Debate on the paradox of clioquinol and SMON, by Dr M.N.G. Dukes
ICP/DSE 166/18 Rev.1	Problems and possibilities of spontaneous reporting systems, by Karl H. Kimbel
ICP/DSE 166/19	Controlled studies, by Dr M. Pfeiffer
ICP/DSE 166/20	Introduction to consensus debate, by Dr G. Kreutz

ICP/DSE 166/21	History and state of adverse drug reaction monitoring in the Federal Republic of Germany, by Dr G. Kreutz
ICP/DSE 166/22	Debate on the long-term safety of antihyperlipidemic drugs lead, by Dr O.R. Oedegaard

Annex 2

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