

Clinical Pharmacological Evaluation in Drug Control

Report on the
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**SEVENTH EUROPEAN SYMPOSIUM ON
CLINICAL PHARMACOLOGICAL EVALUATION
IN DRUG CONTROL**

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1. INTRODUCTION

The Symposium was the seventh in a series of meetings on clinical pharmacological evaluation in drug control, convened annually since 1972 by the WHO Regional Office for Europe, with sponsorship by the Federal Republic of Germany, initially at Heidelberg and later at Deidesheim. Participants have included authorities from the Member States of the WHO European Region and also the United States, WHO regular and advisory staff, and representatives of other organizations.

The meetings have provided a forum for scientific discussion of the clinical problems and procedures associated with drug control in the broadest sense. This activity has complemented the existing regional arrangements for harmonization of drug control legislation and procedures, since such arrangements are largely in the form of treaties or agreements between the regulatory agencies, while the symposia also enlist the cooperation of experts from universities and the drug industry. The work of each meeting has supplemented that of earlier ones and concrete recommendations on general and specific matters have been produced.

The Symposium was attended by 41 participants from 26 countries as well as 20 temporary advisers and regular staff of WHO, and 10 representatives of other organizations (see Annex II).

An innovation in the agenda this year was the discussion of draft guidelines for the evaluation of hypertensive drugs in man, which had been prepared in advance by a working group.

The Mayor of Deidesheim welcomed the participants on behalf of the municipal council, recalling the old adage that good wine — such as that of Deidesheim — makes for good blood and hence for fruitful thinking.

Professor L. von Manger-Koenig, speaking on behalf of the Federal Ministry for Youth, Family Affairs and Health, stressed the value of the meetings in bringing together experts from so many fields and representatives of both eastern and western Europe. The meetings had also facilitated close and valuable personal contacts between those engaged in drug control. The approach adopted at the meetings had contributed to the development of drug legislation and medicine control in a manner which would prove effective in countering abuses and correcting past errors without endangering the progress of pharmaceutical research.

Dr D.K. Sokolov, Director, Development of Comprehensive Health Services, WHO Regional Office for Europe, conveyed a message of welcome from Dr Leo A. Kaprio, WHO Regional Director for Europe. Recalling the worldwide impact of the series of meetings he thanked the Federal Ministry for Youth, Family Affairs and Health for its further generous financial support of the enterprise.

At the suggestion of Dr Sokolov all the participants then introduced themselves individually to the meeting.

Professor F. Gross was elected Chairman of the Symposium and Dr V.K. Lepakhin and Dr K. Türker Vice-Chairmen. The Rapporteurs were Dr Inga Lunde, Professor A. Maleev and Dr M.N.G. Dukas.

In an introductory address Professor Gross observed that there was, logically, a certain cycle of topics in the meetings, since the nature of situations discussed earlier tended to change, and as some problems were solved new ones arose. In particular the legal and ethical aspects of clinical trials had come under much stronger scrutiny than when they were initially discussed in 1972, as had the evident need for improved techniques in selective post-marketing surveillance of drugs.

On the last day of the meeting, Dr Kaprio was present at the Symposium for discussion of the draft report and delivery of the closing address.

2. CLINICAL TRIALS OF DRUGS

2.1 General

Although the need for systematic, quantified and comparative investigation of new drugs in man was recognized by some clinicians early in the present century, the acceptance of the principles and their development so as to produce concrete standards for such work has been surprisingly slow, and much clinical investigation still fails to meet the ideals.

Clinical drug investigations can conveniently be divided into a number of stages, e.g. phases I–IV as defined by the United States Food and Drug Administration or corresponding classifications inherent in the practice of other authorities. The techniques required, such as the use of placebos, and the ethical questions raised by such studies differ considerably from phase to phase. Such classifications should not, however, be rigid since there are in practice transitional situations and work performed in one phase may obviate the necessity for certain investigations in another. Where, for example, particular questions can be adequately handled in phase IV, it is sometimes possible to eliminate this work in phase III. The better the planning and analysis in phases I and II and the better the definition of goals in these phases, the easier it is to design meaningful and specific investigations, avoiding superfluous routines.

The animal toxicity data available before any phase of clinical studies is commenced should be appropriate to that phase, having regard to the limits within which the studies are to be conducted and the nature of the drug. The requirements for data on mutagenicity, fertility, teratogenicity and

carcinogenicity studies were discussed in relation to the various phases of drug development. It is clear that there are considerable differences between the requirements of various regulatory agencies and much further discussion would be required to correct these discrepancies.

Certain general principles are sometimes applicable in setting the proposed human investigational dose on the basis of the effective pharmacological dose in animals, but they must be applied with great caution; the known or anticipated pharmacokinetics of the compound in man as compared with those in the animals studied are likely to be of crucial importance.

The physician administering an investigational drug in early studies in man should be fully informed on all the animal data available, and the physician involved in later phases should be informed as to the animal data and all clinical data obtained in the early phases.

It is essential to ensure that the pharmaceutical formulation of an investigational drug be constant, or that any change be made known to the investigator, since this may have major consequences for the clinical effects of the drug.

The Symposium noted that the severe shortage of clinical pharmacologists and clinical pharmacological centres persists.

2.2 Risks to the subject

The more closely controlled a clinical investigation, the less the risk to the trial subject is likely to be. In practice the risks are the least in phase I studies, since these are often conducted under the close supervision of a clinical pharmacologist and doses used are low.

The need to take certain risks to obtain information must be weighed against the risks to a larger population if a drug is released without the information having been obtained. This is the case as regards patients with liver and kidney diseases; special studies to determine the effects of such diseases on the pharmacokinetics of a drug are necessary if in practice the drug is likely to be taken by such patients. The studies should define if and how the drug can be used in patients with impaired liver or kidney functions.

The development of investigational methods should be directed *inter alia* to the reduction of risks, e.g. by using sequential experimental plans, where these are appropriate, so as to draw conclusions as rapidly as possible and to reduce the number of subjects involved.

The meeting noted that views as to the employment of healthy volunteers in clinical drug studies differ from country to country. Where volunteer studies are permitted, the same guarantees for safety should be provided as those applicable to patients. The performance of studies in healthy children may in exceptional cases be desirable but extreme caution is required and the drug should as a rule already have been studied in adults.

2.3 Planning

The detailed plan of a trial depends in large measure on a careful survey of the information already available from animal and human studies and inventarization of the questions now to be answered, as well as a review of the patients and facilities available.

On this basis it is necessary to ensure:

- (a) An appropriate selection of the standards of reference (placebo or known drug, different doses of the investigational drug).
- (b) Comparability of the groups to be studied with respect to variables which it is not intended to study, but which may affect the findings. Randomization, blocking (stratification) and replication are means to this end. The possibility of interactions must be considered and if possible excluded.
- (c) Statistical evaluation and also a critical methodological assessment of the results.

A checklist is of value in ensuring that the standards are met. It is of great importance to ascertain that the clinicians and other staff are adequately qualified and properly instructed, e.g. as regards the recording of data.

2.4 Goals of successive phases of investigation

The goals of the respective phases of clinical investigation have been defined in many publications, e.g. the Guidelines for Clinical Investigation. Generally speaking the goals are as follows:

Goals of phase I include the study of biological activity, pharmacokinetics, initial dosage and the broad lines of safety and tolerance.

Goals of phase II are to define basic clinical efficacy, optimal dosage in short-term use, pharmacokinetics after multiple dosing, dose-effect relationships, influence of disease states on drug kinetics, and the study of drug interactions whose likelihood can be foreseen.

Goals of phase III comprise the collection, supplementation and confirmation of the information, not obtained in earlier phases, which is required for a decision as to the inclusion of the drug in the therapeutic arsenal and the provision of adequate instructions for its use. Interactions should be studied further. Phase III studies should reflect conditions of practice as closely as possible.

Goals of phase IV are to obtain any additional data emerging when the drug is employed in practice on a large scale, which may affect the delineation of efficacy and safety obtained in phase III, e.g. information on the effects in use over a very long period or on rare but serious adverse reactions or interactions.

2.5 Role of the clinical pharmacologist

The clinical pharmacologist plays an important role in each phase of clinical investigation:

- (a) In *phase I* all work should be undertaken by a clinical pharmacologist or under his direct supervision.
- (b) In *phase II* much of the work, e.g. pharmacokinetic studies, may be undertaken by a clinical pharmacologist and the remainder in close collaboration with him.
- (c) In *all phases* clinical pharmacologists can be involved in the design of protocols and their assessment, and in the selection of doses to be employed, while consulting closely with other specialists who have particular knowledge of the drug field in question.

In addition the clinical pharmacologist can, as an *educator*, ensure that basic teaching on clinical investigation is incorporated into medical teaching, at both the undergraduate and the postgraduate phase. He can also make a more general contribution to the development of efficient consultative procedures in his own country relating to clinical investigation.

2.6 Role of drug control agencies

Before a new drug is investigated in man, it should be impartially assessed to determine its suitability for this purpose. It is desirable to entrust this task to the drug regulatory agency in which the disciplines relevant to the assessment (including toxicology, pharmacology, clinical pharmacology, pharmacy and statistics) are represented, since the agency will in any case be reviewing much of the work at a later phase if the drug is marketed. Such agencies also generally have the necessary administrative machinery to handle the work, but their scientific staff may require expansion for the purpose if unnecessary delays in the processing of applications are to be avoided.

The group was of the opinion that the introduction of procedures of this type should not delay the development of new drugs provided the requirements set for each drug are determined individually.

A drug regulatory agency should be authorized to exercise similar control on phase IV studies, i.e. those involving marketed drugs.

For reasons similar to those given above the drug regulatory agency may be authorized to review the plans and progress of clinical trials of new drugs.

In countries where it is currently not feasible to create a structure such as that outlined above, drug regulatory authorities should at least be informed as to all investigations in progress.

2.7 Role of ethical review committees

Prior review of proposed clinical experiments by an independent institutional committee is highly desirable. Such a committee should be broadly constituted to assess the acceptability of the trial protocol, the adequacy of the clinical supervision and trial facilities, and the ethics of the study as a whole.

Provision should be made for a similar type of prior review of investigations to be conducted outside an institution, e.g. by the individual practitioner; for this purpose it would seem advisable to establish either regional or national ethical committees.

2.8 Role of the pharmaceutical industry

The process of decision-taking in phases, which the investigation and development of a new drug involves, depends to some extent on interactions between the clinical investigator, the pharmaceutical industry and the regulatory agencies.

The physician within industry who coordinates the planning and conduct of research and development in this field plays a crucial role in the process. This applies particularly where trials are conducted internationally, as the physician may have a more complete view of the situation than any other individual and he can ensure that a promising drug is studied by the most capable centres available, irrespective of nationality. As a rule he also has a wealth of data available.

The drug industry too is in an excellent position to contribute to post-marketing surveillance and adverse reaction monitoring since much of the information becoming available on a drug subsequent to its introduction is likely to be submitted by physicians to the manufacturer. In this phase, again, the medical staff of the manufacturing company may be better placed to compile and assess worldwide data than national organizations. There should, however, be close contacts with drug regulatory agencies which should be kept fully informed. International companies should ensure that their branches and representatives receive all relevant information.

The situation sketched above does not entirely apply where, at a national level, responsibility for clinical investigation is exercised by government-sponsored agencies; even here the global view of data which the physician working within an international drug company possesses remains important, so long as adequate publicly sponsored alternatives are not universally available.

2.9 Role of international agencies and other organizations

WHO and other international agencies can play a role in sponsoring clinical investigations of drugs of major importance to public health, e.g. drugs for fertility control and the treatment of leprosy, and of drugs for the treatment of rare diseases.

In addition, a number of nongovernmental international organizations sponsored by medical specialists or associations, e.g. in the field of rheumatism and cancer studies, can coordinate research in collaboration with industry.

In view of the difficulty which some countries, especially smaller ones, may experience in establishing adequate procedures for licensing new drugs for clinical investigation, the Symposium considered that the possibility should be examined of setting up an advisory committee under the auspices of WHO, in which a number of countries could be represented and which would handle such applications confidentially on an international basis and make recommendations to the authorities in the countries concerned.

2.10 Legal and ethical aspects

(1) The rights of the individual subject must be regarded as sacrosanct. There is no other right, e.g. a right to scientific progress, which may be exercised if it impairs these rights.

The principles of the Declaration of Helsinki (1964) as modified at Tokyo (1977) are applicable to all such investigations.

(2) Legal or other binding provisions should ensure that:

- any clinical trial is conducted under competent medical supervision
- preclinical work is adequate
- informed consent is given by all the trial subjects, including those on placebo, preferably in writing
- any risk involved is justified and not disproportionate
- clinical studies are performed according to a scientifically sound protocol.

The last provision should require the termination of the study in certain situations, particularly where severe adverse reactions occur, or the inferiority of the treatment given to one group has been clearly demonstrated.

(3) There should be clear sanctions which can be applied if the above principles are transgressed.

(4) Exceptions to some of these general principles may be made under extraordinary circumstances. In such circumstances, the physician in charge should, if possible, consult others before administering the drug.

(5) The way in which informed consent is to be obtained should be carefully defined *inter alia* as regards the type of information to be given to the patient on the purpose of the study, the nature of the drug and the risks involved; there should be special procedures for consent given on behalf of minors or persons not able to give informed consent, such as mental defectives and unconscious patients.

(6) The investigator bears the primary responsibility for a clinical study. The fact that informed consent has been given does not mean that the trial subject assumes responsibility for the entire risk, nor does the approval given by a review committee or regulatory agency lessen the investigator's responsibility.

(7) In every country there should be provision for adequate and broad insurance of trial subjects (including healthy volunteers and those taking placebo) and prompt compensation for any injury resulting directly or indirectly from participation in the study. Facilities for such insurance should, if necessary, be guaranteed by the state, as is already the case in certain countries.

(8) The manufacturer of an investigational drug has an absolute moral duty and should be legally obliged to provide the investigator with all relevant information on the drug and the work already performed with it. The manufacturer is clearly also liable for any error made by him, e.g. provision of the wrong product.

2.11 Responsibility of governments

As pointed out at earlier symposia, governments should do all in their power to encourage the further development of clinical pharmacology, since the lack of facilities and trained physicians in this field continues to hamper the performance of investigational work and the provision of adequate guarantees on its efficiency and safety.

It is the responsibility of governments to ensure that the legal provisions and procedures specified elsewhere in this section are applied, although the exact arrangements adopted will clearly vary to some extent with the social and political structure of the country concerned.

Governments should work together with clinical pharmacologists and the medical profession as a whole to ensure that the public obtains adequate and balanced information on the need for clinical investigations and the steps which have been taken to exclude unnecessary risks.

3. GUIDELINES FOR CLINICAL EVALUATION OF DRUGS

3.1 Antihypertensive drugs

The Symposium discussed at length draft guidelines for the evaluation of antihypertensive drugs in man, prepared by a WHO Working Group.^a

The guidelines are intended for the clinical investigator carrying out such work rather than manufacturers drawing up applications for the registration of new drugs. However, they might form the basis of guidelines developed nationally or regionally for the latter purpose.

A number of technical alterations were made and certain scientific questions raised during the meeting, all relating to points of detail. Some of the questions were referred back to the Working Group for further consideration. A revised final text was subsequently issued, as presented in Annex I.

3.2 Other drugs

The Symposium urged the development of further guidelines for the clinical investigation of specific groups of drugs. The need to produce authoritative texts in various languages at an early phase was stressed, since much misunderstanding may arise if the translation of drafts is not entirely satisfactory.

Typical topics regarded as of importance include:

- agents claimed to improve cerebral function in the elderly
- anti-arrhythmic agents
- anti-epileptic agents

^a Working Group on the Harmonization of Guidelines for Clinical Trials and Drugs – Antihypertensive Drugs, Uppsala, 24–25 April 1978.

- antirheumatic agents
- anxiolytic drugs
- general principles for clinical evaluation of drugs
- general principles for monitored release
- general principles for monitoring adverse drug reactions
- hormonal contraceptives
- hypnotics and sedatives
- neuroleptics.

In developing such a programme, account should be taken of the guidelines already issued or under consideration by national and regional regulatory or consultative bodies (the latter including the Council for Mutual Economic Assistance, EEC, the Nordic Council and Benelux) and the topics recommended by the Fifth and Sixth symposia.

4. POST-MARKETING EVALUATION OF DRUGS

4.1 Scope and limitations of large-scale multicentre trials

4.1.1 *Antihypertensive agents*

Post-marketing studies can answer questions relating *inter alia* to:

- maintenance of efficacy in long-term use;
- adverse reactions and interactions not identified (or not adequately quantified) prior to marketing;
- effects on the quality of life.

Since hypertensive patients are rarely treated with a single drug, such studies commonly relate to the use of the drug in question in conjunction with others.

Prior to marketing, antihypertensive drugs are generally studied mainly as regards their effects in moderate or severe hypertension. At the present time there is a need for a clearer picture of the value of treating mild hypertension with drugs rather than by general measures alone, and for identifying situations in which hypertension is over- or under-treated.

Much misinformation has been published on the adverse reactions to antihypertensive drugs based on conclusions of spontaneous observation or

uncontrolled work. Open comparative studies may produce valuable information provided they are carefully designed and patient intake is randomized. It may be wise to check patient compliance in populations under study at least making occasional blood and urine tests for the drug or its metabolites. Similar tests may help to detect relevant concurrent medication.

Since many patients have previously received other drugs, these should be recorded so that the cases can be analysed separately.

4.1.2 *Antirheumatic drugs*

Long-term post-marketing studies with antirheumatic drugs are particularly necessary because of the very long period of use of these drugs in practice, the long time-lag before certain of them act maximally, the chronic toxicity of some of the compounds in use, the lack of an adequate experimental model for studying certain of them in animals, and the spontaneous variations in the severity of rheumatic disease in the individual patient. Such studies can also show a decline in the efficacy of a drug in the long term and they are the only way of demonstrating a prophylactic effect or a drug effect on the natural course of the disease. Multiple objective (laboratory) tests, quantified functional tests and direct measures of anti-inflammatory activity (radiology, radio-isotope uptake, infrared radiation from joints) are all desirable parameters in long-term studies.

Common pitfalls are variable patient compliance and unreliability of investigators, who may fail to ensure that the regimen is monitored over a long period.

In a field such as this, international long-term multicentre studies are invaluable and have been initiated under the auspices of the European League Against Rheumatism (EULAR), being complemented by specific drug investigations of other types. Such studies can be conducted by ideally equipped centres and provide comparative data on a series of drugs, indicating the relative merits of each and its place in the total therapeutic arsenal. Despite some variations in the way in which drugs are used in various European countries, it is possible to establish a common protocol. It is essential to standardize as far as possible the other forms of therapy being administered concurrently, e.g. physiotherapy. Interference by intensive non-medical therapy among hospitalized patients provides a good reason for performing part of this work among outpatients. There should be a critical centralized analysis of the data to ensure optimal reliability.

4.1.3 *Hormonal contraceptives*

Since hormonal contraception may be used for as much as 30 years, long-term assessment of its wanted and unwanted effects is essential. Experience to date confirms that certain types of adverse reaction may not be identified, or their clinical importance determined for many years. In view

of the type of adverse reaction which might be anticipated in the long term (e.g. malignancy, effects on metabolism and on the vascular wall), careful examination and history-taking must be done at the time of admission, so that possible predisposing factors can be recorded for reference during subsequent analysis of the adverse effects. The prior hormonal contraceptive history is especially relevant, since many users of a given product have previously employed a different one.

One important parameter in the study is the termination rate, which can indicate major adverse reactions or contraceptive failure. Studies need not be comparative.

Limitations of such studies relate to:

- their confinement to selected centres capable of optimal collaboration, in that such centres may not in fact be treating a typical population in a manner such as that used in the field;
- the sample size, which even in ambitious studies may be too small to detect low-incidence long-term risks such as neoplasia;
- the fact that the subjects involved have generally themselves selected the products which they use, so that randomization is not possible.

Studies such as those sponsored by WHO on a worldwide basis must take into account differences in populations, conditions of life, nutrition and incidence of endemic disease.

For the study of possible carcinogenic effects, specific case-control or cohort studies must be conducted over a period of 15 years or more.

5. VALUE OF EPIDEMIOLOGICAL APPROACHES IN MONITORING OF ADVERSE REACTIONS

5.1 General

In studying the possibility that a drug may have adverse reactions not identified at the pre-marketing stage, it is necessary to observe "adversities" or "adverse events" occurring during its administration, irrespective of whether any causal link is suspected or not.

Various techniques for the detection and study of adverse reactions are available and are discussed below; they should be regarded as complementary to one another.

The introduction of certain sophisticated systems may involve considerable effort and expense and the relative value of each must be carefully

and constantly evaluated if proper priorities are to be set and a balanced complex of techniques developed.

Whilst new drugs are most likely to require intensive study, attention must also be devoted to certain potentially toxic older drugs for which new uses have been found, e.g. penicillamine or levamisole.

It is generally difficult to obtain sufficient information on adverse reactions to free-sale preparations used for self-medication, e.g. because the physician is not aware of their use and they are not recorded in prescription registers. However, some of the ingredients are also prescribed by physicians and hence information on their adverse reactions can be obtained.

5.2 Cohort studies

Cohort studies may be conducted prospectively or retrospectively. The prospective method, although of great value in a well-defined field of interest, is unsuitable for investigating very rare or long-term adverse reactions because of the loss of subjects from the study over a considerable period. Such reactions are better investigated by retrospective studies.

5.3 Monitored, recorded and controlled release

The techniques under this heading, discussed in detail at earlier symposia, are of value when, at the time of introduction of a new drug, there is reason to anticipate an unusual pattern of adverse reactions, e.g. when the drug differs substantially in its properties from any employed earlier. It is important to use the techniques selectively because they involve considerable effort and they have technical limitations in that there may be no control group. It may also be difficult to maintain the interest of physicians in providing information over more than a brief period and they may object to participation, fearing that the system would bring on loss of confidentiality or prescribing freedom. Such objections may even lead physicians to prescribe other drugs.

5.4 Spontaneous monitoring

Spontaneous monitoring may be regarded as a means of obtaining early warnings on adverse reactions and it has been of value in identifying particular reactions. It may indicate the frequency of a given side-effect provided the reporting rate and the prescribing figures are known. Costs are low but it is important that a higher proportion of physicians understand the objectives of such monitoring and recognize their responsibility to report.

The method may also prove of greater value if physicians become accustomed to reporting adverse events as described above, or unexplained symptoms, as well as merely suspected adverse reactions. In principle a much wider range of reports should be attracted by adverse reaction monitoring centres

than those reaching the literature, since it is simpler for the reporting physician to notify a centre than to compile a formal letter or paper for a journal.

To avoid repetitive reporting, it may be useful to indicate in general terms certain types of information which need not be reported, e.g. well-known minor effects of widely used drugs.

Means should be studied of making the reporting procedure as attractive and simple as possible, for reporting physician's feedback of information, and periodic publication of reports can do much to motivate them to continue to collaborate and the centre should be capable of providing answers to their questions. There should be appropriate exchanges of information with industry as complementary data are often available to both parties.

The work of national centres is to some extent mutually complementary, since certain adverse reactions are observed much earlier in some countries than others and may indeed be more frequent in some because of genetic differences.

Drug monitoring centres should regard it as part of their task to ensure that the public has a balanced view of the adverse reactions problem and is aware of the work being done to define and avoid risks in this field.

5.5 Intensive hospital monitoring

This monitoring is feasible only at certain centres but can provide both early warnings and quantitative data on adverse reactions, though the population involved is unlikely to be typical of the patient population at large.

If chance associations are to be avoided, adverse events have to be recorded in depth, with full attention to the time sequence, the exact nature of the event (so that it can be linked with possibly relevant data in the literature) and the nature of the underlying disease (which may be responsible for the event). An important requirement is that clinical events be assessed by more than one clinician to avoid observer bias.

Two somewhat different approaches may be discerned: one in which adverse events as such are recorded and large volumes of data possibly suitable for statistical analysis are obtained, and the other in which a limited range of suspected adverse reactions is studied in depth and the ultimate assessment of a possible cause-effect relationship is a matter of clinical judgement.

Provided requirements such as those listed above are met, intensive monitoring, despite its non-comparative character, can be an important instrument in detecting adverse reactions, particularly as regards hospital populations, and the establishment of programmes in this field is to be encouraged.

5.6 Casual observations

Casual observations reported in the literature are to be welcomed but it is evident that their anecdotal character should be borne in mind and that

the material in question should be critically reviewed from time to time if a cumulation of fictions is to be avoided (see also section 5.8).

5.7 Medical record linkage

Medical record linkage may supplement the techniques discussed above. Use is made of existing registers (e.g. of cancer cases, causes of death or congenital malformations), drug utilization records and prescription data of the type available to a national health service or a publicly owned pharmacy corporation.

The value of this approach has been demonstrated in the study of specific points, e.g. the hypothesis that there is a link between breast cancer and reserpine. It is particularly suited to the detection of long-term adverse reactions of low incidence.

Advantages include the possibility of nationwide coverage, the relatively low cost and the ability to obtain and analyse data rapidly when a suspicion arises. Disadvantages include the fact that the material is, in part, not drug oriented.

Problems arise with respect to confidentiality of information on the individual patient and to differences in the manner in which data are recorded and patients identified. Only a few countries have so far succeeded in overcoming these problems to any appreciable extent, but they are certainly not insuperable.

It is to be noted that record linkage requires close centralized control of information and that small countries with a public health care system are those most likely to succeed in creating highly developed programmes in this field in the near future.

5.8 Drug literature

The drug literature contains much repetitive data on adverse reactions as well as some poorly founded material. The useful role of the journals is, in fact, fourfold:

- (a) *Casual observations* can be published, which may stimulate discussion in medical circles and may elicit further reports of the same type, leading to a rapid confirmation or refutation of the suspected causal link.
- (b) *Quantified data* can be published from specific studies of adverse reactions already known to exist.
- (c) Reports of suspected adverse reactions received by *monitoring centres* can be published, preferably when there is reason to suspect a causal link and also to stimulate further reporting.

(d) *Critical reviews* of the literature, particularly reviews of anecdotal reports, can be published in order to distinguish fact from fiction.

Editors of medical journals should be encouraged, when publishing new data on adverse reactions, to ensure the provision of prior data which may be relevant (e.g. that available in the literature or with regulatory agencies or drug firms), so that the new report can be seen in its correct context. The non-drug literature may be relevant, particularly if the effect observed has been described earlier as "idiopathic".

5.9 Role of WHO

There is currently some duplication of work, in part unavoidable, between adverse reaction monitoring centres as regards specific studies which they conduct and reports which they issue. The Symposium noted with approval the current redevelopment and expansion of the international monitoring system for adverse reactions to drugs, now based in a WHO collaborating centre in Uppsala. In the framework of this programme, a greater degree of coordination between national centres should be attainable.^a

Countries not currently participating actively in the programme should seriously consider doing so, and a closer link between it and intensive monitoring projects should be established. The Symposium noted that the relationship between the programme and the pharmaceutical industry is currently being investigated, with a view to using the information available to both parties as efficiently as possible, while respecting the need to regard as confidential data which are provided as such.

6. RECOMMENDATIONS

6.1 Clinical trials of drugs

(1) Since the shortage of trained clinical pharmacologists and of facilities for their work remains the greatest obstacle to the performance of efficient and safe clinical investigations of drugs, governments should give high priority to the development of training and career openings in this field as specified at earlier symposia.

(2) Drug regulatory agencies should be accorded authority and staff to assess the suitability of new chemical entities for clinical investigation in man. The approach should be flexible so as to avoid undue delays and to specify

^a WHO Technical Report Series, No. 498, 1972.

requirements for pre-clinical work which are adapted to each drug in question. Since in some countries the creation of such a regulatory structure is hardly feasible at the present time, the possibility should be examined of establishing a committee under WHO auspices to advise the authorities on individual applications for investigational drug licences. As a transitional measure, governments should at least ensure that drug regulatory agencies are fully informed as to studies currently in progress.

(3) Procedures analogous to those outlined under (2) should be established for licensing new clinical studies with drugs already marketed.

(4) The information provided to physicians conducting clinical investigations should be more complete than is often the case as regards pre-clinical and clinical studies with the drug in question, the pharmaceutical formulation (and any change introduced therein) and the need to adhere strictly to the protocol.

(5) Ethical committees should be established, preferably on a local or regional basis, to assess the ethical, legal and scientific merits of proposed clinical trials.

(6) Further attention should be given to the design of clinical experiments in order to reduce risks to the trial subject, e.g. by developing designs which render it possible to limit the scope and duration of studies.

(7) Legal or other binding provisions should ensure that clinical studies are conducted only for sufficient reason, that the risks are acceptable, that informed consent is obtained, and that the principles outlined above and those inherent in the Declaration of Helsinki (1964), as modified at Tokyo (1977) are respected.

(8) Governments, the medical profession and clinical pharmacologists should work together to ensure that the public obtains adequate and balanced information on the need for clinical investigations, and the steps which have been taken to exclude improper and disproportionate risks.

(9) Measures taken to protect patients acting as trial subjects should also be applicable to healthy volunteers, if these are to be involved.

(10) Facilities for the comprehensive insurance of the subjects involved in clinical trials are essential and should, if necessary, be guaranteed by the state.

6.2 Post-marketing evaluation of drugs

(1) Better integration of all types of information becoming available on a drug subsequent to marketing (e.g. from planned studies, spontaneous

reporting in the literature as regards efficacy, and the various sources of data on adverse reactions) is essential if the use of a drug is to remain fully in accordance with current knowledge.

(2) For drugs which are likely to be administered for many years, studies of very long duration are necessary to obtain data on any change in efficacy, effects on the quality of life, and long-term adverse reactions and interactions.

(3) The planning of long-term post-marketing studies of efficacy is often less than ideal, and investigational techniques for this purpose need to be further developed; both open and blind trials in this phase can provide better data than are usually obtained, e.g. with antihypertensive and antirheumatic drugs or hormonal contraceptives. Checks on patient compliance should be included.

(4) Multiple drug comparisons over a long period should be conducted, e.g. under the sponsorship of scientific associations, to complement the drug studies sponsored by industry and to provide data on the relative place of each drug in therapy.

(5) For drugs in long-term use, international multicentre studies are needed to determine the extent to which the effects are ultimately influenced by national and regional factors.

6.3 Monitoring of adverse drug reactions

(1) As with efficacy data, information on adverse reactions to drugs on the market should be better integrated than is currently the case, so as to make full use of all the sources of information available and enable conclusions to be drawn more rapidly.

(2) Means to render spontaneous reporting of adverse reactions more attractive for the physician and more effective for the community should be studied.

(3) The experience with medical record linkage already obtained in a number of countries should be analysed to determine the extent to which corresponding techniques can be employed elsewhere as a means of identifying those serious adverse reactions to drugs which are relatively rare and occur only after prolonged administration.

(4) The role of the medical literature in adverse reaction reporting deserves careful study, since much valuable information is currently obscured by the presentation of invalid and repetitive data.

(5) The current development of the international monitoring system for adverse reactions to drugs, based in Uppsala, should be regarded as an opportunity to broaden its basis so as to make use of sources of information other than those provided by national centres, e.g. information available to industry.

6.4 Guidelines for clinical evaluation

(1) Guidelines for the clinical investigation of specific groups of drugs, such as those already drafted by the WHO Working Group on the Harmonization of Guidelines for Clinical Trials of Drugs – Antihypertensive Drugs, should continue to be developed and issued in the form of recommendations to medical investigators.

(2) National and regional agencies developing guidelines for the clinical aspects of new drug applications should be encouraged to take into account WHO recommendations and guidelines issued by other agencies, in order to avoid unnecessary discrepancies.

7. TOPICS FOR DISCUSSION AT FUTURE MEETINGS

While recalling that the Sixth Symposium had already listed a large number of topics deserving consideration at future meetings,^a the present Symposium felt that the following should be added.

7.1 General themes

Themes touched upon during the meeting or proposed by participants as requiring more detailed discussion included:

- the legal situation of the experimental clinical pharmacologist;
- a comparison of the drug information flow to physicians in various types of society;
- strict liability of manufacturers with respect to clinical investigations;
- the process of informed consent by the trial subject;
- drug studies in patients with liver and kidney diseases;
- ethical constraints on the physician employed by the pharmaceutical industry, or by drug control agencies;
- discrepancies between regulatory decisions (case histories);
- the ethics of promotional research;
- the concept of “essential drugs” in developed countries;

^a See Clinical pharmacological evaluation in drug control: Report on a Symposium. 1977 (ICP/PHA 004).

- assessment of old combined preparations;
- quantification of the repercussions of drug control measures on community health.

7.2 Specific themes

Future meetings should devote one or more sessions to the consideration of draft guidelines, prepared by a working group in advance, on the clinical investigation of specific groups of drugs (see section 3.2).

Annex I

GUIDELINES FOR EVALUATION OF ANTIHYPERTENSIVE DRUGS IN MAN

1. Introduction

Drug treatment reduces morbidity and mortality in hypertensive patients. Clinical evaluation of potentially useful drugs for this purpose should follow generally accepted scientific principles as laid down in WHO Technical Report Series, No. 403 (1968)^a and No. 563 (1975)^b. In the present report those principles are presented in the form of guidelines for the clinical investigator.

2. Early studies in man

2.1 First administration to man/pharmacodynamic studies

Such studies can be carried out either in healthy volunteers or in patients with mild hypertension, with no additional risk involved. The results of animal studies showing the type of action should, preferably, be available. Early human studies should attempt to confirm animal pharmacology. Side effects and pharmacodynamic effects of different doses should be evaluated. Pharmacokinetic studies are desirable. If they are not possible, adequate pharmacodynamic measurements may provide the necessary information. Pharmacokinetic measurements must be validated by pharmacodynamic assessment. This ensures that the presence of an active metabolite or prolonged receptor binding after plasma clearance is not overlooked. Time of onset, magnitude and duration of the activity of various doses should be investigated after single and repeated administration.

2.2 Pilot therapeutic trials/dose-finding studies

The principles for selection of patients should be the same as for controlled clinical trials (see below). In the initial placebo period (or baseline treatment if placebo treatment alone is considered to be unethical), blood pressure should be stable (see para. 3). The frequency of administration is

^a WHO Technical Report Series, No. 403, 1968 (*Principles for the clinical evaluation of drugs*. Report of a WHO Scientific Group).

^b WHO Technical Report Series, No. 563, 1975 (*Guidelines for evaluation of drugs for use in man*. Report of a WHO Scientific Group).

initially determined according to the duration of action in man. If the drug is given infrequently (e.g., once a day), the effect should be measured just prior to administration and the subsequent dose. Initial dosage should commence at a low level and appropriate increments be made at suitable intervals. If a maintenance dose has been reached which is well tolerated and effectively lowers blood pressure, it cannot be concluded that the same dose would be well tolerated at the start of treatment. Dose-response relationships should be established in patients with varying severity of hypertension. Side-effect assessment and the usual safety evaluation should be performed (see below). The requirements for animal toxicology testing are discussed in WHO Technical Report Series, No. 341 (1966).^a Antihypertensive drugs are usually administered for prolonged periods. It is therefore necessary to conduct toxicological studies of adequate duration before long-term evaluation is commenced. Studies of too short duration may force cessation of successful therapy.

3. Controlled therapeutic trials

Formal therapeutic trials should be performed only if the initial studies have suggested that there could be a useful therapeutic effect. They should be planned and carried out according to recognized scientific criteria.

Drugs not primarily intended to be used alone (e.g., a peripheral vasodilator causing reflex tachycardia and increased plasma volume) can be evaluated in combination with other agents counteracting some of the unwanted haemodynamic effects.

Note: If at any time during a therapeutic trial blood pressure rises to an unacceptable level, the patient should be put on an established form of therapy.

3.1 Methods of observation

3.1.1 Blood pressure and heart rate

Blood pressure should preferably be measured by the same observer using a standardized procedure at a standardized time. It is recommended that blood pressure and heart rate be measured both in the supine (usually 2–3 consecutive measurements after a standardized time), and in the upright position (usually one single measurement after one minute standing), and it is desirable also to repeat the measurement at the end of a simple exercise test. If the results of such a test give rise to concern, it is advisable to repeat the measurements during and after a standardized ergometric test.

^a WHO Technical Report Series, No. 341, 1966 (*Principles for preclinical testing of drug safety*. Report of a WHO Scientific Group).

The value of the methodology for blood pressure measurement specified in Technical Report Series, No. 168 (1959)^a is reaffirmed, while recalling the additional comment made by the WHO Expert Committee on Arterial Hypertension and Ischaemic Heart Disease (1962)^b on the desirability of using an instrument that reduces observer bias.

Blood pressure should be recorded as exactly as possible, usually to the nearest 1–2 mm Hg.

When measuring the blood pressure, the observer should not know the values obtained in the previous series of observations, to avoid bias.

Chemical and haematological investigations (including examination of the eye ground) need to be carried out at appropriate intervals according to the stage of development of the drug. Physical examination, chest X-ray and electrocardiogram are required only at the start or at the start and at the end of the trial.

More frequent monitoring of the electrocardiogram during the first week of treatment may be advisable if the drugs used are known to adversely affect intracardiac conduction or cardiac performance.

3.1.2 Side effects

The evaluation of the drug should include questions giving the patient an opportunity to report side effects. Check lists may also be used, provided a placebo period is included in the study. The use of a check list may, in the absence of a placebo period, lead to the recording of an unduly high side-effect rate. Consideration should be given to the subjective feelings of the patient, which might be quantitatively expressed using various methods (e.g., analogue scales).

3.2 Criteria for admission of patients

It is desirable that criteria for admission be laid down to ensure that the patient population is appropriate. Care has to be taken not to give a new drug to a “negative selection” of patients who are resistant to all the other already available drugs. Deviations from defined criteria will not necessarily invalidate the trial, but may reduce its sensitivity. Reasonable limits for the blood pressure of patients to be included in the trial and acceptable variations on 2–3 separate occasions during a placebo period may be as follows:

^a WHO Technical Report Series, No. 168, 1959 (*Hypertension and coronary heart disease: classification and criteria for epidemiological studies*. First report of the Expert Committee on Cardiovascular Diseases and Hypertension).

^b WHO Technical Report Series, No. 231, 1962 (*Arterial hypertension and ischaemic heart disease: preventive aspects*. Report of an Expert Committee).

- average supine diastolic pressure of 96–104 mm Hg, maximum variation of 10 mm Hg;
- average standing diastolic pressure of 105–115 mm Hg, maximum variation of 14 mm Hg.

At higher values, a prolonged placebo period is not recommended. The placebo period should be prolonged until the variation comes within the figures indicated. Any decline in standing diastolic blood pressure between the last two readings should not exceed 5 mm Hg. This assumes special importance with blood pressures at the lower end of the range.

Patients showing a greater decline should have an extended placebo period.

3.3 Types of controlled therapeutic trial

There are several types of controlled therapeutic trial in hypertension, depending on the questions to be answered.

3.3.1 Placebo controlled trials

Two main designs for placebo controlled trials (and also for comparative controlled trials – see para. 3.3.2) are used, i.e. “between-patients” (parallel group trials) and “within-patients” (cross-over trials). After an initial placebo period, patients are randomly allocated to one of the two treatment groups. In a “between-patients” trial, one group continues treatment with the placebo and the other receives active therapy. In the “within-patients” design, all patients receive both the placebo and active therapy for given periods of time. Half of them first receive the placebo, and the other half active treatment. Both approaches are useful, and both have advantages and disadvantages. The “between-patients” design requires a greater number of patients. It is important in a “within-patients” trial to give adequate attention to the duration of antihypertensive action, i.e. the periods of assessment have to be of sufficient length to exclude carry-over effects. In using drugs suspected of causing withdrawal reactions or rebound effects in “within-patients” trial an appropriate “tapering-off” period should be included. It should be noted that blood pressures upon administration of placebo in those patients receiving it second may be lower than in those receiving placebo first. It is important that the drug be studied in optimum dosage (see para. 3.3.2).

3.3.2 Comparative controlled trials

Though double-blind placebo controlled trials provide information on antihypertensive effect, comparative evaluation with existing drugs of established value may yield information of greater importance. The two types of trial mentioned in para. 3.3.1 can be used, i.e. the “between-patients” and “within-patients” designs.

For a comparative controlled trial, it is most important to study drugs in optimal dosage. This can be done in different ways:

- (a) dose titration before the study proper;
- (b) fixed dose increments during the trial proper (every patient receives the whole predetermined dose range);
- (c) individual dose titration during the trial proper (every patient receives dose increments according to his blood pressure response).

3.3.3 Long-term trials

Long-term therapeutic trials of antihypertensive agents are mainly required to exclude development of tolerance (loss of antihypertensive effect) and to monitor delayed adverse reactions. The same criteria for admission and the standardized procedure to be used apply to these trials. Checks may be spaced at less frequent intervals (i.e. 1–2 monthly when suitable). Laboratory tests may be done with progressively longer intervals (e.g., prior to treatment at 1 month, 3 months, 6 months, 1 year and thereafter yearly). These long-term studies should be performed in at least 100 patients for one year. If such trials are set up as multicentre-trials, particular attention should be paid to meticulous standardization and coordination.

4. Drug interactions

Such interactions may be divided into adverse drug interactions, mostly occurring with other drugs used for concomitant diseases, and favourable interactions of a combination of antihypertensive drugs. Interactions should be looked for in the course of the therapeutic trials; if there is any evidence that they will occur, they should be properly investigated. Special attention should be paid to possible interactions with drugs commonly used in hypertensive patients.

Annex II

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