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INTERNATIONAL MONITORING OF ADVERSE REACTIONS TO DRUGS

PILOT RESEARCH PROJECT FOR INTERNATIONAL DRUG MONITORING

Progress Report by the Director-General

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INTRODUCTION

1. In its resolution EB43.R17[1] the Executive Board, emphasizing the importance of the pilot research project aimed at the establishment of an international system for monitoring adverse reactions to drugs, requested the Director-General to keep the Board and the Assembly informed of the progress of the project. Accordingly, this report on the Pilot Research Project for International Drug Monitoring (IR 0531) has been prepared.

2. In resolution WHA18.42[2] the World Health Assembly had requested the Director-General "to study further the requirements of an international programme for the collection, analysis and dissemination to Member States of information on adverse drug reactions". Following the recommendation by a WHO Scientific Group, the World Health Assembly in resolutions WHA19.35[3] and WHA20.51[4] then requested that a pilot research project for the establishment of an international system of monitoring adverse reactions to drugs should be carried out utilizing funds provided by the Government of the United States of America for this purpose.

THE PURPOSE OF MONITORING

3. The primary objective of drug monitoring for adverse reactions is to identify at the earliest possible time the liability of a drug to produce undesirable effects which have not been detected during clinical trials. As had been pointed out by the first WHO Scientific Group on Monitoring Adverse Reactions in November 1964, many adverse effects of drugs in man are not predictable by toxicological experiments on animals or controlled clinical trials, if such effects occurred infrequently, if the populations exposed to the drug differed from the population participating in the clinical trial in characteristics such as age, sex, disease, pathology and genetic characteristics, or if the specifications of a drug were modified subsequent to the trial. A systematic follow-up of drugs after their introduction into general use is therefore essential, but it was only after the thalidomide experience that the need has been generally recognized for planned surveillance of drugs in respect of their potential to cause serious adverse reactions.

4. Recognition of the frequency and severity of adverse drug reactions grew at a time when powerful drugs were being produced in ever increasing numbers and variety. Drug induced disease has become a serious problem as is illustrated by the following quotation:

> "Perhaps some 5% of the beds in our general hospitals are occupied by patients suffering to a greater or less extent from our efforts to treat them. Yet the incidence of adverse reactions to drugs is not well known and even major reactions often go unrecognized. Indeed one of the urgent tasks confronting us today is to put such reactions on a sound epidemiological basis. Thus their collection, tabulation, and analysis on a national and ultimately on an international scale are of great importance."[5]

It has therefore become clear that medical treatment with any drug demands a knowledge of its adverse effects as well as its therapeutic effectiveness. Incomplete knowledge of the frequency and severity of adverse effects of drugs is a major weakness of modern therapeutics and appreciation of this fact has led to the establishment in a number of countries of systems of monitoring drugs for suspected adverse reactions.

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[1] Handbook of Resolutions and Decisions, 10th ed., p. 114.

[2] Handbook of Resolutions and Decisions, 10th ed., p. 112.

[3] Handbook of Resolutions and Decisions, 10th ed., pp. 112-113.

[4] Handbook of Resolutions and Decisions, 10th ed., p. 113.

[5] Dunlop, Sir Derrick (1969) Brit. Med. J., 2, 622.

PROGRESS OF THE WHO PILOT PROJECT

Aims and objectives

5. The aim of the pilot project has been to investigate the feasibility of an international drug monitoring system along the lines of the Director-General's report to the 37th session of the Executive Board[1] and in accordance with the following objectives:

(a) assess the feasibility or otherwise of an international system of drug monitoring;

(b) develop the methodology for recording case histories of adverse reactions to drugs, systems for analysis and feed-back of data to national monitoring centres;

(c) undertake analysis of instored data on an experimental basis;

(d) provide facilities for searches by WHO staff and national centres on the types and patterns of adverse reactions to individual drugs; and,

(e) make a preliminary study of the contribution of drug monitoring to research in pharmacology and therapeutics.

6. In January 1968 WHO established the WHO Pilot Research Project, which is located in Alexandria, Virginia, United States of America, to study the collection, analysis and dissemination of information on adverse reactions to drugs based on reports received from national centres.

National Monitoring Centres

7. Ten countries (Australia, Canada, Czechoslovakia, Federal Republic of Germany, Ireland, Netherlands, New Zealand, Sweden, United Kingdom of Great Britain and Northern Ireland and United States of America) with established drug monitoring systems agreed to participate in the Pilot Research Project by forwarding to the WHO Pilot Centre case reports of adverse reactions recorded in their national centres. The pilot study has been based so far on 23 000 case reports received in the WHO Centre up to December 1969.

8. For participating national centres the following criteria as recommended by the WHO Scientific Group on International Drug Monitoring in 1965, were adopted:

(a) a designated national mechanism or system responsible for monitoring and obtaining data on suspected adverse drug reactions;

(b) continuity of staff and services for collecting, verifying and storing reports of adverse reactions;

(c) a national standard for terminology and identification of drugs;

(d) facilities and ability for examining the validity of reports, and for detailed study, when necessary, of reported adverse reactions; and,

(e) availability of data on drugs used nationally, and the ability to estimate the extent of drug usage.

9. The majority of national monitoring systems depend upon the spontaneous reporting of suspected adverse reactions to drugs by physicians to a national drug monitoring centre. Careful validation of the data is required, after which analyses and further investigations are carried out to confirm or refute the association between a drug and a suspected reaction.

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[1] Off. Rec. Wld Hlth Org., 148, Annex II.

The methods adopted by any national centre for this purpose depend upon conditions within the country and vary according to the drug, the reaction, and the population at risk. For example, prospective and retrospective surveys are used, as well as intensive monitoring in hospitals (WHO Technical Report Series No. 425).

10. The problem of adverse reactions to drugs exists in all countries and because the detection of some serious adverse reactions requires reports to be obtained from large populations, the need for international co-operation soon became obvious.

WHO Pilot Centre

11. Since the establishment of the WHO Centre, as requested by the World Health Assembly in resolution WHA20.51,[1] there has been rapid development. The organization for receiving reports from national centres, coding and filing them, and preparing appropriate computer programmes is fully functional on a pilot scale. The project maintains close contact with the national centres.

12. The staff of the WHO Centre has prepared and adopted methods of processing, recording, storing, linking and retrieving reports. Methods have also been developed to facilitate the validation and evaluation of data. Dictionaries of preferred terms for adverse reactions and a classification of drugs formulated for recording and linking data within the project have already been of considerable help to the national centres and will be of great help to countries which establish monitoring centres in the future. These compilations have also facilitated the exchange of information between national monitoring centres and WHO.

13. One of the primary objectives of the WHO Centre is to serve as a signalling system for drug and adverse reaction associations. In order to accomplish this, there must be minimal time lapse between the occurrence of the reaction and its evaluation. The time periods that exist between the onset and WHO computer filing of the adverse reaction are being closely studied. The national centres are assisting the WHO Centre by providing estimates in these parameters of their national reporting trends. Other forms of data input, such as punched cards or magnetic tapes, are now being considered by some national centres. If this form of data is pre-coded, e.g. by adverse reaction preferred terms, etc., manual data handling could be significantly reduced. The WHO Centre is now ready to assist any national centre in the development of such computer programmes.

14. The initial computer programming system enabled summary documents to be sent to national centres in March 1969. Constructive review of these led to revision and further development. Improved documents were distributed in September 1969 based on 11 000 case reports. The circulated computer printouts have detailed:

(a) frequencies of reactions recorded for each drug;

(b) frequencies of drugs associated with each reaction, these including cumulative totals over various periods;

(c) condensed summaries for rapid reference; and,

(d) drug reference lists compiled from reports by participating countries.

Suitable statistical methodologies are being explored so that meaningful associations can be elicited from the data for presentation to national centres.

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[1] Handbook of Resolutions and Decisions, 10th ed., p. 113.

CONTRIBUTIONS OF THE PILOT PROJECT TO OTHER WHO PROJECTS

International Classification of Diseases

15. This publication heretofore has not had a sufficiently detailed or comprehensive section to provide a uniform terminology of adverse drug reactions and classification. During the course of the pilot project, terminology has been developed to serve this need. Since the terminology and classification of the pilot project have been based on an international collection of data, they will provide the basis for the preparation of terminologies to be incorporated into revised editions of the International Classification of Diseases.

Drug dependence

16. Drug dependence is recognized as a serious adverse reaction to a number of drugs used therapeutically. Case reports of drug dependence and related reactions to psychotropic drugs, particularly those associated with new drugs, reaching the WHO Centre will be of interest to many countries, to the Drug Dependence Unit of WHO, and to other international organs concerned with drug abuse and its control.

Congenital malformations and human genetics

17. The occurrence of congenital malformations associated with the administration of certain drugs during pregnancy has been well documented. However, the relationship of drugs to several of the more commonly occurring malformations, e.g. cleft palate, has not been fully determined. There is evidence that genetic material in germ cells may be changed by exogenous influences including drugs. Reports of abnormalities compiled in drug monitoring centres and in registries of congenital malformations should be linked for the study of possible relationships between drugs and malformations. Certain adverse reactions, such as those occurring within ethnic groups or suspected of being caused by anomalies of drug metabolism, will be of interest in the field of human genetics.

Clinical pharmacology

18. Drug monitoring can produce the suspicion that a cause and effect relationship exists between a drug and an adverse reaction. Confirmation of such relationship should come through detailed study of the biological effects of the drug in man. The work of the WHO Centre will present the clinical pharmacologist with many new ideas for the elucidation of the mechanisms of adverse reactions and orientate the clinician towards a more rational basis for therapeutics and safer use of drugs.

BENEFITS TO OTHER COUNTRIES (Non-contributors to the project)

19. Although input of records to the WHO Centre must be primarily from countries that have gained experience of collecting and handling information at the national level, the benefits have much broader implications.

20. Information on drug reactions derived from the WHO Centre can be expected to augment drug safety evaluation in countries with national monitoring systems participating in the project. Subsequent action taken in one country under the terms of resolution WHA16.36[1] (which requests Member States to communicate to WHO decisions to prohibit or limit the availability of a drug causing a serious adverse reaction) can then be transmitted by WHO to other Member States.

21. Several of the major drug developing and exporting countries are at present participating in the project. An effective international monitoring system will raise the standards of safety in the choice of drugs available on the world market and in their methods of administration. All other countries stand to gain by the earliest possible recognition of hazards encountered in countries which initially use a new drug.

[1] Handbook of Resolutions and Decisions, 10th ed., p. 111.

POSSIBLE FUTURE DEVELOPMENT OF THE PROJECT

22. The intent of the pilot project has been to carry out a feasibility study with the aim of developing an international system for monitoring adverse reactions to drugs using information derived from national centres. The pilot project has demonstrated that an international drug monitoring system, based on the processing, storage, recovery and linkage of data on adverse drug reactions provided by national centres, is a practicable undertaking.

23. The methodology of rapid notification of the reports from participating countries to the WHO Centre has been devised on a pilot scale and can be expanded to absorb the total output of each centre. Computer techniques have been formulated for handling large amounts of available data allowing early review of possible associations between drugs and reactions together with the feed-back of this information to national centres.

24. A Meeting of Investigators in September 1969, and a Meeting of Consultants on International Drug Monitoring in November 1969 reviewed the progress of the pilot project. Based on the evidence provided, on the analysis performed and on the recommendations made by these groups, the following course of action may now be envisaged.

25. The project could move into a "primary operational phase". This primary operational phase would largely be concerned with consolidating the achievements so far and creating the organization needed for the routine handling of all monitoring records submitted by the participating countries.

26. Provision should be made for a comprehensive assessment of technical progress prior to fully operational status. Due to the urgent need for a fully operational system, the recommended assessment would occur no later than three years after entering the primary operational phase.

27. The major objective of the WHO drug monitoring programme is the improvement of rational therapeutic practice throughout the world by the identification and, when practicable, the avoidance of adverse reactions to drugs.

28. The pilot project has already made considerable progress in the development of drug reference lists and of classifications for drugs and adverse reactions. The development of further computer programmes for routine analyses, alerting signals and special searches should be continued during the primary operational phase.

29. The Pilot Research Project has established a nucleus of trained staff, but assurance of continuity into a new phase needs to be established. Suitable measures for the participation of additional national centres would be required in the future. Modifications to the organization and methodology of the project would need to be undertaken as the number of national drug monitoring centres increases.

30. The work of the WHO Centre is likely to be of particular benefit to any participating country whose national centre only receives relatively small numbers of reports, for it could draw on the data available at the Centre to supplement its own reports. Situations are expected to arise in which a few reports of an adverse reaction to a drug occurring in different countries could be adequately appreciated only when collated at the WHO Centre. In addition, collated reports, involving new drugs released for marketing would be of considerable value, both in respect of countries in which the drug is available and in those in which it has not yet been released. Suitable statistical methodologies would continue to be explored so that meaningful assessment could be made from available data.

31. Exchange of experiences between the drug monitoring project and other Divisions of WHO should benefit this programme, as well as encourage development of monitoring systems in other contexts.

32. Once the WHO Centre is in the primary operational phase, all countries, including those not participating directly, would be able to benefit. By augmenting drug safety evaluation in countries with national monitoring systems, more meaningful information on drug hazards could be provided by WHO to all Member States.

FINANCIAL REQUIREMENTS

33. The pilot project has been developed under the grant provided by the Government of the United States of America,[1] for a three-year period extending from 1968 to 1970.

The grant expires on 9 May 1970, at which time the pilot project will have come to an end, as originally planned.

34. It will be incumbent upon the Twenty-third World Health Assembly, on the basis of the assessment report which will be submitted to it by the Director-General, to make a decision as to the possible future development of the project into a primary operational phase, as outlined above in paragraphs 22 to 32, including related financial requirements.

35. The financial requirements of a primary operational phase are estimated at US$ 230 000 for the remainder of 1970; US$ 304 000 for 1971 and US$ 312 000 for 1972, i.e. a total amount of US$ 846 000 for a three-year period.

36. Continuation of the project into its primary operational phase, after the present grant expires on 9 May 1970, cannot be envisaged unless further contributions to the Special Account for Medical Research are forthcoming.

Keeping the above in mind, and subject to the decision of the World Health Assembly, the Director-General has forwarded to the Governments of the 10 countries whose national centres have participated in the pilot project, full details on the results achieved to date with a request for advice of their continuing interest and willingness to make contributions to the Special Account for Medical Research.

Responses to this inquiry will be provided to the Board, if available at this session, and to the World Health Assembly, for their consideration.

[1] cf resolution WHA20.51, Handbook of resolutions and decisions, 10th ed., p. 113.