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INTERNATIONAL DRUG MONITORING - WHO PILOT RESEARCH PROJECT

REPORT OF A MEETING OF CONSULTANTS

Geneva, 17-20 November 1969

DMO/69.3

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INTERNATIONAL DRUG MONITORING - WHO PILOT RESEARCH PROJECT

A meeting of consultants was held in Geneva from 17-20 November 1969 to review future developments in international drug monitoring, with special reference to the WHO Pilot Research Project, in the light of the present situation in the field. Dr L. Bernard, Assistant Director-General, opened the meeting and expressed appreciation for the attendance of experienced consultants to advise WHO on its future programme for drug monitoring.

1. THE PRESENT POSITION OF INTERNATIONAL DRUG MONITORING

1.1 The purpose of monitoring

The primary objective of monitoring patients and drugs for adverse reactions is to define at the earliest possible time the liability of a drug to produce undesirable effects which have not been detected during clinical trials.

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."⁽¹⁾

Recognition of the frequency and severity of adverse drug reactions grew at a time when drugs, pharmacologically active and therapeutically effective, were being produced in ever increasing numbers. The thalidomide disaster emphasized that unless preventive action is taken, further disasters will occur. More recently, 3,500 deaths are estimated to have occurred in one country among patients using pressurized aerosols containing sympathomimetic amines for the treatment of bronchial asthma⁽²⁾.

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.

(1) Dunlop, Sir Derrick (1969) Brit. Med. J., 2, 622

(2) Inman, W.H.W. and Adelstein, A.M. (1969) Lancet, 2, 279

1.2 National monitoring systems

Most national 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. The methods adopted by any national centre for this purpose depend upon the country concerned 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 hospital monitoring (WHO Technical Report Series No. 425).

The problem 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.

1.3 International co-operation in monitoring

WHO has established a Pilot Research Project to study the collection, analysis and dissemination of information on adverse reactions to drugs, based on reports from national centres. A report of a meeting of investigators⁽¹⁾ describes in detail the methods developed and adopted. The WHO Pilot Project now provides the Drug Monitoring Unit of the Division of Pharmacology and Toxicology of WHO with a tool by which the work of the national centres could be enhanced. This development was clearly necessary to allow national centres access to information on larger populations, to improve communications between centres, and to provide them with technical advice and help.

1.4 The future of monitoring

Adverse reactions to drugs have become a health problem of great magnitude. Whatever form international co-operation in this field takes, many more countries will wish to participate in such a programme. The likelihood is that the methods used will in time become more refined so as to improve the quality of data, and its analysis and interpretation.

It should be pointed out that the purpose of monitoring drugs for adverse reactions is not their removal from therapeutics but rather their use in a more informed and thus more rational manner.

The development of national and international systems of drug monitoring will most likely be accompanied by the emergence of departments of clinical pharmacology in hospitals and universities in many countries and each of these developments will stimulate the other. It is predicted that the study of adverse reactions to drugs will become an increasingly important part of therapeutics in the next decade.

(1) WHO Pilot Research Project for International Drug Monitoring; Report of a Meeting of Investigators, September 1969 (DMO/69.2)

2. THE WHO PILOT RESEARCH PROJECT

It was in the light of the above review of the current situation and their predictions for the future that the consultants considered the WHO Pilot Research Project.

2.1 The Report of the Meeting of Investigators (DMO/69.2, Sept. 1969)

The consultants had before them the report of the Meeting of Investigators at Geneva on 22-27 September 1969 which studied the development of the WHO Pilot Research Project for International Drug Monitoring (DMO/69.2). They were favourably impressed by the technical achievements of the project. These reflect great credit on its staff and the report provides evidence of the substantial contribution which has already been made by the project to the problems of monitoring adverse reactions to drugs.

The consultants agreed with the conclusions reached by the report and made the following comments.

2.2 Operational progress (DMO/69.2, item 3)

The consultants noted the important work of developing methods of processing, recording, storing, linking and retrieving reports which is described in Appendix C. Methods are also being developed to facilitate the validation and evaluation of data. Dictionaries of preferred terms for adverse reactions and a classification of drugs have already been of considerable help to the monitoring centres of nations participating in the project and will be of great help to nations which establish national centres in the future. They have also facilitated the exchange of information between national centres and WHO.

2.3 Future development of the project as an operational centre (DMO/69.2, item 4)

The consultants studied this section of the report with considerable interest. They suggested that methods for the selection of reports for onward transmission to WHO by the national centres should continue to be studied lest the WHO Centre be overwhelmed with unessential data. It may also be necessary to consider for what period of time reports on adverse reactions should be retained in the computer store.

The consultants observed that the phrase "early warning", although now in common use, is a misleading one. They suggested that this should be replaced by a term* which is better suited to a situation in which the number and/or nature of reports of suspected adverse reactions to drugs are such that the WHO Centre or a national centre sees a need for further enquiry. It would not normally be until such further enquiry had been carried out and the findings interpreted that any decision concerning a drug would be undertaken.

* It was proposed that the term should include the word "Signal" which should be qualified by an adjective or proper name. Since a suitable adjective could not be found at the meeting, a proper name was proposed which would obviate interpretive and language difficulties. The name chosen was "Halbach" because of Dr Halbach's contribution in this field and thus the term will be a "Halbach Signal". In English this term has the added advantage of connoting the "haulback" of information for further study and enquiry.

The intent of the Pilot Project was 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. Situations will doubtless arise in which a few reports of an adverse reaction to a drug occurring in different countries could be adequately appreciated as a cause of anxiety only when collated at the WHO Centre. In addition, a national centre will need frequently to review its own data on a suspected reaction in the light of the collated information available from the WHO Centre.

The work of the WHO Centre is likely to be of particular benefit to any participating country whose national centre receives relatively small numbers of reports, for it can draw on the data available at the Centre to supplement its own reports. Once the WHO Centre is fully operational, all countries, including those not participating directly, will be able to benefit.

As the international drug monitoring programme evolves, the possibility of detecting delayed adverse reactions such as foetal abnormalities or carcinogenesis should be investigated.

The consultants agreed that Intensive Hospital Monitoring should be developed as is described in the WHO Technical Report No. 425. It can make an important contribution to spontaneous reporting systems and be of use in evaluating suspected associations between drugs and adverse reactions. They welcomed the interest in this shown by the Pilot Research Project and the significant contribution which the project can make to standardize the methods used in intensive hospital monitoring and to facilitate communication between the centres where it is initiated.

There is a need to develop optimum methods of disseminating information to all nations about adverse reactions to drugs and about decisions which are taken by national centres.

2.4 Contributions to other projects (DMO/69.2, item 5)

The consultants believed that the development of the terminology of adverse reactions and the drug reference list has been extremely important. The International Classification of Diseases should be revised in the light of this development. This would be a major contribution to the future of monitoring of adverse reactions to drugs. The therapeutic and pharmacological classification of drugs, which has been developed by the Pilot Project, was part of a working document studied and well received by the EURO symposium on the Consumption of Drugs held in Oslo in November 1969. Furthermore, lists of preferred terms for adverse reactions and the drug classifications are likely to enhance the value of many varieties of drug statistics.

3. OBJECTIVES FOR INTERNATIONAL DRUG MONITORING

The major objective of any drug monitoring programme must be the improvement of rational therapeutic practice throughout the world by the identification and, when practicable, avoidance of adverse drug reactions.

As contributions to this, and in the light of experience gained in the Pilot Research Project, the immediate aims should be:

3.1 To develop methodology

The Pilot Research Project has achieved much in the development of drug reference lists and of classifications for drugs and adverse reactions. The development of computer programs for routine analyses, alerting signals, and special searches should be continued.

3.2 To establish an operational system

The Pilot Research Project has established a nucleus of trained staff, but assurance of continuity into a new phase is now essential. The Drug Monitoring Unit should also plan for participation of additional national centres, and for such adjustments to the organization and methodology as this may require.

3.3 To disseminate information

Accumulated information must be made available quickly and effectively. Detailed study will be necessary if the ultimate aim of appropriately informing all Member States is to be achieved.

3.4 To relate the project to other WHO activities

Exchange of experiences between the Drug Monitoring Project and other Divisions of WHO may benefit this programme, as well as encourage development of monitoring systems in other contexts. This should be facilitated by eventual location of the project in Geneva.

3.5 To stimulate other drug monitoring programmes

Existing systems of intensive hospital monitoring can contribute valuable information that will aid evaluation of the evidence from the reports submitted by national centres. The WHO Drug Monitoring Unit should continue to encourage the establishment of hospital or other programmes for specific purposes.

3.6 To increase awareness of the problems of adverse reactions

The attention of the medical and allied health professions needs to be drawn to the importance of observing suspected adverse reactions to drugs and the ethical duty of the professions to report them.

4. RECOMMENDATIONS

The consultants recommend, on the basis of their review of pertinent documents and their deliberations, as follows:

4.1 Establishment of operational programme

The project should move into the primary operational phase as discussed in the September report of the technical advisers⁽¹⁾. Provision should be made for a comprehensive assessment of technical progress prior to fully operational status.

(1) WHO Pilot Research Project for International Drug Monitoring; Report of a Meeting of Investigators, September 1969 (DMO/69.2)

Due to the urgent need for a fully operational system, the recommended assessment should occur no later than three years after entering the primary operational phase.

4.2 Technical recommendations

The consultants accepted the technical recommendations made in the report of the September meeting of technical advisers, specifically the recommendations 7.3 to 7.7 of that report quoted under the following headings:

Objectives (7.3)

"(a) In particular, effort should be concentrated on the exploitation and further development of the already very effective computer programming system and the establishment of routine production of standard analyses and feed-back to national centres. To this end, note should be taken of many suggestions on points of detail made during the meeting, as a basis for experiment rather than firm recommendation.

(b) Special attention should be given to the development of automatic signalling procedures that will draw attention to problems as soon as the cumulative evidence justifies this, and that will then initiate searches of the data for interpretative purposes.

(c) The staff of the WHO Centre should continue to undertake research on their files of data and on methods of processing records, with a view to further improving the system as a whole. For example, investigation of the quality of assessments of reaction severity, differences between different national experiences, and contributions from follow-up records are needed."

Evaluation (7.4)

"WHO should arrange for periodic meetings of a small group of consultants, comprised of experienced officers in national centres, to evaluate the most recent output from the international centre and to advise on current developments."

Communication (7.5)

"The WHO Drug Monitoring Centre should continue to act as a channel for the exchange of information between national centres, and should encourage in every way possible the formal and informal communication between centres that has already produced great benefits."

Intensive monitoring (7.6)

"Intensive drug monitoring in hospitals and the community within the province of national centres should be co-ordinated by WHO when it is appropriate to develop programmes internationally. Reporting from intensive monitoring systems should be used to augment the WHO early warning network."

Participation (7.7)

"The WHO Centre should consider the incorporation of further countries with suitable national centres or special centres for drug monitoring, and should be prepared to advise such national or special centres on appropriate methods."

4.3 Interchange of personnel

A programme should be established to promote the interchange of personnel between national centres and the international centre to achieve:

- (a) a greater understanding of the problems unique to each level;
- (b) greater compatibility in the handling and processing of data among the various centres, and,
- (c) improved communications.

4.4 Transmission of information to Member States

At the appropriate stage of development of the international centre a system should be established for the transmission of pertinent information to all Member States, whether or not they operate national centres.

4.5 Educational measures

Measures should be taken to increase the understanding of adverse reactions, including but not restricted to:

- (a) Publications about the WHO programme and associated projects in standard medical journals and related media;
- (b) Inclusion of instruction on adverse reactions and monitoring procedures at all levels of medical education, and,
- (c) Facilities for temporary attachment of suitable persons to the WHO Centre in order that they may later aid in the establishment of monitoring projects in their own countries. This will include regularly established fellowship programmes or ad hoc programmes.

4.6 Meeting of consultants

Meetings additional to those specified in recommendation 7.4 of the September report should be arranged so that the opinions of users of output from the system and others not intimately involved with the operation of national centres may provide a broader perspective.

ACKNOWLEDGEMENT

The meeting acknowledged the valuable co-operative efforts of the ten national drug monitoring centres and also the substantial support provided by the Government of the United States of America without which the achievements of the pilot project would not have been possible.