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Harmonized Studies on Organophosphorous Pesticide Poisonings

Report of an Intercountry Workshop
Bangkok, Thailand, 8-9 March 2000

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1. INTRODUCTION

Organophosphorous (OP) Pesticide Poisoning is a major health problem and a leading cause of death in the countries of the South-East Asia Region and a number of controversies exist on the most effective treatment. The Regional Director WHO, South-East Asia Region (SEAR) therefore, agreed to provide support for the study and organization of a workshop on this issue.

The workshop was organized in collaboration with the Medical Toxicology Unit, Guy's and St Thomas' Hospital (London, UK), on behalf of the WHO South-East Asia Regional Office (SEARO). Dr Jenny Pronczuk from WHO, HQ/IPCS [1] participated and provided continuous technical support. The workshop was hosted by the Institute of Health Research, Chulalongkorn University, Bangkok, from 8-9 March 2000. Dr L. Szinicz (Germany) and Dr Palarp Sinhaseni (Chulalongkorn University) opened the meeting and welcomed participants. Dr Szinicz Chaired the meeting and Dr Pronczuk acted as rapporteur. Dr Volans acted as co-rapporteur.

2. OBJECTIVES

The objectives of the workshop were to:

(1) To review and evaluate the results from a retrospective study on OP pesticide poisoning;
(2) To discuss the existing health care facilities in the SEA Region and the means of enhancing their capabilities and capacities to participate in harmonized studies;
(3) To explore the possibility of prospective studies on OP pesticide poisonings: feasibility, objectives, protocol(s) and strategy;

[1] The International Programme on Chemical Safety (IPCS) is a joint venture of WHO, ILO and UNEP, administered by WHO/HQ through the Programme for the Promotion on Chemical Safety (PCS) and which collaborates with SEARO programme for Sustainable Development and Healthy Environments for Promotion of Chemical Safety activities in SEAR countries.

(4) To evaluate internationally agreed, peer-reviewed guidelines for the treatment of OP pesticide poisonings and their applicability in SEA countries, and
(5) To develop initial plans of action for prospective studies on OP pesticide poisonings and recommend a strategy.

See Annex 1 for the agenda and programme of the meeting and the List of Participants is at Annex 2.

3. DISCUSSIONS

Dr Pronczuk stressed that in view of the large number of cases of OP poisoning treated in health facilities in countries of the SEA Region, a coordinated multicentre study could provide valuable information to improve patient management at the country, regional and global levels. Collaboration among a few selected hospitals could allow the harmonized collection of large number of cases annually and enhance their capacity to compare effectiveness of treatments, improve patient management, rationalize the selection and use of antidotes and other pharmaceuticals and also demonstrate the costs of medical care and loss of days of productivity. Furthermore, it would facilitate scientific communication through the use of harmonized language and definitions and enhance the capacities of countries in the prevention of poisoning. The IPCS severity grading system and INTOX software have the potential of being adapted to the needs of OP case data collection and analyses. Issues raised at the WHO consultation on OP pesticide poisoning studies *(Geneva, June 1999*) and followed up at the INTOX Working group (*Guaruja, Brazil, October 1999, available in http://www.intox.org/intox11)* were presented. The harmonized treatment scheme for OP pesticide poisoning cases is available in the Poisons Information Monograph (section 10), which was distributed to participants

Dr Karalliede presented the results of a retrospective study on OP pesticide poisoning to assess the situation in selected SEA countries. This was used as baseline information for the discussion on the planning of prospective studies and identification of main needs and constraints. The pilot collaborative retrospective study on OP pesticide poisoning was undertaken by the Medical Toxicology Unit (MTU), London, on behalf of WHO/SEARO with technical support from WHO/IPCS, HQ, Geneva. The Munich Poisons

Centre and the Institute of Pharmacology and Toxicology, German Armed Forces Medical Academy, Germany collaborated in the initial preparatory phase of the project (preparation of the harmonized data collection format). Findings of the retrospective survey demonstrated that:

- OP poisoning continued to be a major health problem in the Region (e.g. leading cause of hospital death in Sri Lanka). The vast majority of poisonings followed oral ingestion of the liquid form with suicidal intent and occupational exposure was greatest in Thailand. Accurate statistics for prevalence would be difficult to obtain unless institutions providing private medical care and traditional medicines were included in the study along with records of coroners and police surgeons.
- A wide range of OP pesticides were used in the Region and in most instances of poisoning, the identity of the OP agent involved was not known with certainty, resulting in deficiencies or delays in management. There was little or no information available to clinicians on the physical characteristics or chemical nature of the pesticides used in the Region available to clinicians.
- Several therapeutic regimens were in use within institutions and within countries. There were no nationally or regionally agreed protocols for management of OP poisoning. A major drawback was the non-availability of basic drugs (e.g. atropine) and facilities (e.g. for gastric lavage) in many of the peripheral hospitals. The lack of mechanical ventilators and shortage of drugs and related facilities necessitated the movement of patients to better equipped hospitals at considerable human and economic cost.
- There were no established programmes for continuing medical education in toxicology in general and for OP poisoning in particular within the Region. From the information available, toxicology was not recognized as a speciality by the universities or postgraduate institutions in the countries visited.
- Following OP poisoning, the greater number of patients were managed by resident medical staff who were dependent upon their exposure to toxicology at medical school and on outdated medical texts to manage patients.
- Facilities for biochemical investigations and for identifying OP agents were most limited and restricted the care afforded to patients.

The different needs for a prospective, coordinated, multicentre study on OP pesticide poisonings were discussed.

Dr Zilker made a presentation on the physiological basis of the treatment of OP poisonings (OPP) and the way these poisoning cases were diagnosed and treated in Munich, Germany. Although some general principles were agreed upon, physicians tended to follow their own criteria in the treatment of OPP. Most poisonings were on account of parathion, metasystox and dimethoate (main OP pesticides used in the country), and were usually suicide attempts. The cases of diethyl-parathion poisoning were very severe, required ventilation, a long stay in the ICU and had a high fatality rate (41%). Oximes were effective, unless extremely high doses of the pesticide were taken. Reference was made to the different values of plasma and red blood cell (RBC) cholinesterases and their reactivation, and also about the persistent inhibitory activity detected in plasma of same cases. With the demethon-methyl OPs intoxications the evolution is less severe, but the use of oximes seems to be less effective. The efficacy of oximes depends not only on the type of OP involved but also on how early it was administered (this is related to aging of the enzyme). It was stressed that more clinical cases are required to prove the efficacy of oximes. Dr. Zilker presented an overview of the main elements to consider in the treatment of OPP: gastric lavage (to be done early, within the first four hours and with protection of airways), induction of vomiting (contraindicated), charcoal administration (could be useful only if repetitive), cathartics (harmless but useless), haemoperfusion (not indicated), control of convulsions (with diazepam), sedation during artificial ventilation (using fentanyl, midazolam, barbiturates and pancuronium bromide if necessary), atropine (in high doses, titrated, in bolus and followed by continuous infusion), oximes (only obidoxime available in Germany), sodium bicarbonate (if pH lower than 7.3, only to correct acidosis), parenteral nutrition, antibiotics and mucolytic agents. The necessity, opportunity and type of analytical and biomedical studies required were presented. Measurement of RBC cholinesterases is the best parameter to follow up poisoning cases.

Discussions were centred on the value of measuring RBC and plasma cholinesterases, and also on their costs, as both analyses are important in proving the efficacy of treatment with oximes, and good quality analytical procedures are required. It was stressed that there is no proof of the efficacy of activated charcoal in reducing the adsorption of OPs (in vivo). The

indication of gastric lavage (GL) with or without intubation was discussed, as in countries of the Region; GL is done very frequently in conscious patients (with previous intubation only if the patient has elements of CNS depression). The main problem of GL in the non-intubated patient is aspiration pneumonia due to the solvent. The measurement of OPs in blood requires sophisticated methods, but is feasible in frozen plasma samples, and the possibility of having sample analyses done in a central laboratory (that could also do the quality control for other laboratories) will be considered.

Dr Szinicz presented a list of the main points of a clinical trial protocol, as stated in the WHO guidelines (25 points listed), as well as those to be added in multicentre studies. This adds extra complexity to the proposal and requires very careful consideration. The Case Report Form (CRF) of a study on the "Monitoring of Cholinesterase Status in Patients with OP Pesticide Poisoning for Assessment of Therapeutic Measures" (on going in Germany) was presented as an example, with details on how and where the study is performed. It was agreed that the main objective of this workshop was to discuss and agree upon the hypothesis of the study and its feasibility. Biostatistical input would be required from the beginning of the study, to ensure that the number of cases allowed sound conclusions to be reached.

Dr Surjit Singh (Chandigarh, India) gave a presentation on the comparison of aggressive atropinization and conventional doses of Pralidoxime (2-PAM) vs. aggressive atropinization along with continuous Pralidoxime infusion in patients with severe OP pesticide poisoning. Chandigarh is 240 km north of Delhi and has a Postgraduate Institute of Medical Education and Research, with a university teaching hospital with 1,200 beds. Two studies using different protocols for 2-PAM administration and atropinization were undertaken. The first study (January 1990-December 1992) involved 18 patients with respiratory failure who required mechanical ventilation (8-10 ml tidal vol/kg body weight with respiratory rate 8-10). They were given one gm 2-PAM at onset, one gm after 30 minutes and one gm after 12 hours. The dose of atropine was maximal on day 1, and mean dose was 178.9 mg (range 60 to 480 mg), and then gradually reduced. The mean duration of mechanical ventilation was 53 hours and mean duration of atropine treatment 9.6 days (range: 1 to 24 days). Fourteen out of 18 patients survived. In the second study (July 1997-December 1997), 16 patients were given atropine 5mg at onset and 2.5 mg every 5 to 10 minutes till atropinization, along with 2-PAM in continuous infusion 500 mg/hr (7.5 mg/kg

body weigh). The total dose of atropine was 735.02 mg (SD ± 742.98) (range: 85-3000mg) and the dose on day 1 was 181.43 (SD ± 129.45) mg. The duration of mechanical ventilation was 131.5 ± 95.65 hours (range: 10-336). Fourteen out of 16 patients survived. It is quite possible that 2-PAM improves the outcome in patients with severe OP pesticide poisoning cases requiring mechanical ventilation.

Dr Szinicz made gave a presentation on the potential advantages of the use of oximes in three clinical cases studied. Reactivation of RBC cholinesterases in vivo and ex-vivo shows that reactivation and fast recovery is possible in cases presented. Obidoxime was effective in severe poisonings when the dose absorbed was relatively low. In cases of so-called "megadose" exposure, reactivation was achieved only several days after the exposure. Obidoxime was ineffective in oxydemethon methyl poisonings when more than one day had elapsed. The results of a study on exposures to dimethyl phosphoryl compounds and diethyl-phosphoryl compounds were presented, as well as recommendations for administration of obidoxime.

Discussions followed on the opportunity and efficacy of gastric lavage, the importance of measuring RBC cholinesterases and the laboratory and quality control implications, on the correlation between clinical features and enzymatic reactivation, on outcome of patients. Also on the laboratory facilities required: where and how to measure enzymatic inhibition and the need to ensure quality control. The German protocol presented is extremely detailed and might be difficult to apply in hospitals which do not have all the facilities required. However, as it has gone through in depth review and has already been tested, it was considered as a good basis for planning a study and adapting it to the needs and conditions of the participating countries. Several hypotheses were discussed. It was agreed the study would be on the efficacy of oximes in reactivation of RBC Cholinesterase and its correlation with clinical status in OP pesticide poisoning.

Dr Szinicz introduced the points for discussion in the working groups and it was proposed that the WHO requirements and the CRF of the German study protocol be reviewed by participants. Modifications into the title of the study proposed were introduced and finally approved as: *A multicentre SEA study on the effects of oximes on red blood cell cholinesterase activity and clinical status in acute OP pesticide poisoning.*

The primary objective of the study would be to evaluate the efficacy of oximes in reactivating phosphorylated RBC cholinesterase and identify the factors that influence reactivation. The secondary objective would be to improve the management of patients poisoned by OP pesticides. Reference to specific oximes could be made later on as it was not relevant at that stage. It was noted that countries using oximes had only pralidoxime and that Nepal was the only country without a regular supply of oximes. No obidoxime was used in SEA countries. The endpoints of the study would include reactivation of RBC cholinesterase and clinical outcome. The subpoints of clinical status would include: dose of atropine required, survival, duration of artificial ventilation, and time of extubation. The value of adding the assessment of muscle power was discussed. The devices for measuring neuromuscular conduction may be too expensive and complex to use. Other simpler methods could be eventually considered for the study. The study design was open, prospective, multicentre, and observational (non-interventional).

Concerning sample size, an expert in biostatistics and study design would define the lowest number of patients required to ensure validity of the study. It was estimated that the number of severe cases (requiring mechanical ventilation) per year would be approximately 10 in Kathmandu, 25 in Mumbai, 20 in Chandigrah, 30 in Bangkok and 10 in Colombo. Sample size could be approximately 100, but many different active principles would have to be considered due to the very large variety of OP pesticides used in the countries. Study population should be only adults, from 18-65 years of age. However, it was considered that cases aged below 18 could eventually be included, if necessary and feasible from an ethical point of view.

Inclusion and exclusion criteria were discussed in detail. The use of artificial ventilation was an inclusion criterion, but it might represent a limitation to the study, as ventilators were unavailable in many hospitals. Inclusion criteria were: evidence of exposure (history or suspected OP exposure); severity of exposure (intubation, with or without artificial ventilation, and unconsciousness with Glasgow coma scale less than 8), and age above 18 years or below 65 years of age. Exclusion criteria were: indication of exposure to carbamate pesticides or mixed poisoning; life-threatening event; administration of any blood product and derivative, and pregnancy. Issues for further discussion were: opportunity for pregnancy tests, HIV detection, pre-existing pathologies, problems related to shipment of samples and their costs. Aspiration pneumonia was not an exclusion criterion.

The importance of having the prior informed consent for each case registered was stressed (further information on this issue and on the proposed study protocol will be obtained from relevant WHO divisions).

The methods of data analysis and interpretation would be considered with the biostatisticians. Publication of results should be done as a Project Group, as this would allow the inclusion of all participants. Coordinators of the country studies would be able to use the data collected for the preparation of other studies and their publication (in consultation with the Project Group). Dr. Sinhaseni stressed the importance of following Good Clinical Practice principles. Dr. Volans referred to the need to prepare training material for those who would be involved in the implementation of the project.

Concern was expressed on the costs of such a study. Some resources might be available, but it was foreseen that a project proposal would be prepared and submitted to potential donors. Dr. Pronczuk clarified that cost estimates of the project would include all items, including pharmaceuticals, laboratory material, computers and software, transportation of samples, time and expertise for data collection, entry and analyses and other items, even if already available at the study sites. Professionals to be involved included the coordinator, a part-time research medical officer, a nurse coordinator and analytical technician. Special arrangements would be explored in countries where several hospitals would be involved in data collection (e.g. Thailand and Sri Lanka) and international coordination required. Dr. Zilker proposed that a pilot study be done with few cases in order to test the CRF and also demonstrate the feasibility of the study.

Specific analytical studies required included the measurement of RBC and plasma cholinesterases, and detection of OP pesticides in biological fluids. Availability and costs of OP detection would be explored by Dr Zilker and Dr Volans, and by representatives of participating countries, and consultation would take place with advisors of the IPCS Analytical Working group WHO/HQ (and contact points in SEARO). The issue of which laboratories would be selected and involved would be decided once information on the subject was made available. It would be essential to obtain a list of OP pesticides used in each country. The issue of cholinesterase determination was raised, was the RBC cholinesterase method and other analytical procedures had to be harmonized, and the specific storage

conditions for transportation considered. India and Nepal are interested in doing their own laboratory studies, as well as Thailand, but this could be done in coordination with a central reference laboratory in Germany or the United Kingdom. Dr Szinicz stated that Professor Eyer (Germany) offered to train technicians in the use of the laboratory techniques required for measuring cholinesterases. Other issues addressed by the group were: specification of age of the patient, amylase and lipase determination, C reactive protein. It was proposed that participants test the existing protocol in order to assess its applicability, identify the main constraints encountered and propose the modifications required. Participants agreed to undertaking such a study, seen as very useful for their countries and were eager to contribute actively.

4. RECOMMENDATIONS

(1) Participants from countries should revise the German Study protocol in detail and test with a few real cases and send their comments and suggestions to Dr Szinicz (cc. Karalliede and Pronczuk).

(2) The background and first draft of the study protocol should be prepared through consultation of the MTU, WHO, IPCS and the German OP Study group with the assistance of a biostatistician, and circulated to project participants for review and discussion (through e-mail discussion).

(3) Cost estimates should be prepared once the draft protocol ready and complied with the existing regulations on studies involving human subjects. In due course participants will be requested to provide information for budget preparations (local costs which should include cost of drugs like PAM which is not readily available in many institutions).

(4) WHO IPCS/HQ will send the relevant WHO documents on Good Clinical Practice and Research Projects, and the PIM on Organophosphorous Pesticides to participants.

(5) WHO IPCS/MTU/SEARO will explore the possibility of a meeting for detailed final discussion on the protocol before mid-2000.

(6) The final report of the meeting will be circulated to colleagues developing the SEAR analytical toxicology activities (Dr Braithwaite, Dr Widdop, and Dr Kumari) and also to Dr Eyer (in Germany).

5. CLOSING SESSION

At the closing session of the workshop, Dr Karalliede thanked the very active involvement of the participants who provided the data for the retrospective study and participated in the discussions. He also thanked Dr Sinhaseni for the the excellent support provided by the Institute of Health Research. Mr Terrence Thompson stressed the importance of this project and the relevant role played by the MTU in organizing the workshop. Dr Szinicz thanked all participants for their input and for the interest expressed in the study. Dr Pronczuk stated the main recommendations and thanked Dr Karalliede for the intensive work of data collection, and the staff of the Institute for their very valuable support in the organization of the workshop.

6. ACKNOWLEDGEMENTS

The support of Dr J Pronczuk, WHO IPCS/HQ and MTU in preparing the draft workshop report is thankfully acknowledged.

Annex 1

PROGRAMME

8 March 2000

09.00	Opening
09.15	Objectives of the meeting
09.30	Presentation of the study protocol, planning and implementation of the retrospective study on OP pesticide poisoning
10.30	Presentation of the results of the retrospective study
11.00	Plenary discussion of the retrospective study: lessons learned
13.00	Analysis by participating health facilities: main difficulties encountered and needs for implementing harmonized studies.
14.00	Presentation of existing internationally harmonized guidelines on the treatment of OP pesticides poisoning
14.30	Discussion on the harmonization of treatment guides according to the needs of health facilities in the countries.
15.30	Exploring the possibility of a prospective studies on OP pesticide poisonings: definition of objectives and strategy.
16.00	Presentation of existing protocol(s) on prospective OP pesticide studies
16.30	Identification of terms of reference for Working Groups

9 March 2000

09.00	Working Groups on: (a) Preparation of a harmonized prospective study and its protocol (b) Implementation of a prospective study: How? Where? When?
10.30	Working Group (continuation)
13.00	Discussion/Working Groups on: (c) Initial plan of action and recommended strategy
15.30	Plenary presentation and discussion on items (a), (b) and (c)
16.45	Conclusions and recommendations
17.15	Closing ceremony

Annex 2

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