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Report of Visit to Japan (Wednesday 16 August - Wednesday 23 August): L L Smith

General Comments

I was impressed by the level of understanding of the toxicology of paraquat in ICI (Japan). Bill Riddell, Kamishikiryosan and Takeisan (Takeda Chemicals, but at present situated in ICI (J) Offices) were familiar with the problem of toxicity and the recommended treatment. They had been briefed some months previously by M S Rose and J K Howard on the emetic formulation and were familiar with its properties. They impressed on me the particular difficulties of discussing toxicological or registration problems in Japan since the governmental system was very much 'closed' as compared with Western Europe or the United States. They indicated that any change in the formulation of Gramoxone which required registration would take perhaps years to process. This is of particular importance to the introduction of safer formulations of Gramoxone.

I think it is advisable that ICI (J) should meet and discuss with toxicologists and medics associated with the Ministry of Health and Welfare to explain the problems of paraquat toxicity. The major problem in Japan is the number of fatalities, largely resulting from the intentional ingestion of Gramoxone. I neither saw nor heard anything to indicate that this number is likely to fall (other than by chance) and if anything, in the next few years, they may actually increase. It is, therefore, important to educate the Ministry of Health and Welfare of the problem and of our basic contention that the removal of Gramoxone would not alter the total number of suicides but only redistribute the deaths to other causes. It is, perhaps, significant that with the withdrawal of parathion from the Japanese market so the number of fatalities from Gramoxone have increased.

Background

My visit to ICI (J) was the result of their request that a toxicologist familiar with paraquat toxicity and the use of emetic in paraquat formulations should visit Japan. In early August ICI (J) learned that the Japanese Ministry of Health and Welfare was considering the reclassification of paraquat, from the 'deliterious category' to either 'poisonous substance' or 'specified poisonous substance' category. This latter category would effectively classify paraquat out of existence. The object of my visit to Japan was two-fold:- (1) to meet with toxicologists who are known to advise the Ministry of Health and Welfare to ensure that their appreciation of paraquat toxicity was accurate, and (2) to discuss with ICI (J) and the distributors of paraquat ways in which paraquat fatalities might be reduced.

Thursday 17 August (am)

Present: Bill Riddell, Michio Kaneda, Kamishikiryosan

I was briefed by Bill Riddell on the Japanese situation and we agreed that it would be sensible if I could meet with as many toxicologists advising the Ministry of Health and Welfare as possible. This was Kamishikiryosan's responsibility. We discussed the problem of paraquat fatalities which are now numbering in excess of 100 per annum in Japan. I was given the impression that the major problem is to reduce the number of fatalities since only this is likely to impress the regulatory authorities. We discussed the effect of the changes in the distribution of Gramoxone in Japan which ICI (J) already have in progress. These include (1) no longer selling Gramoxone in 100 ml containers (already in practice), (2) the replacement of 300 ml containers with 1 litre containers, (3) label changes.

We discussed the possibility that changing the label to provide a specific warning that Gramoxone is poisonous may 'advertise' the product to the would-be suicides. I think that in the Japanese context this is a very important point. The ICI (J) view was that there is little knowledge of how toxic Gramoxone is within the population. This means that the present suicide rate is the result of a general impression amongst would-be suicides that pesticides can kill. If this is the case it is simply the large number of containers of Gramoxone available in domestic situations which makes it of likely use in suicide attempts; hence the rationale of attempting to sell fewer items by increasing the volume of Gramoxone in each container. The situation in Japan may therefore be similar to that in the UK in the late 1960's. Our experience at CTL strongly suggests that as Gramoxone (paraquat) was given publicity as a highly toxic substance often causing fatalities so the incidence of its use as a suicidal agent increased. Certainly it is the case that the number of suicides dramatically increased in the 1970's with little or no change in the accident rate. I, therefore, feel it is very important to be aware of the possibility that raising the level of awareness of the population to the intrinsic toxicity of Gramoxone may increase the number of fatalities as a result of suicide. I can only advise as strongly as possible that this situation is given careful consideration.

We also discussed other means of making Gramoxone safe. Although the inclusion of the emetic should be beneficial I cautioned ICI (J) that they should not be over-optimistic as to the likely decrease in fatalities as a result of its inclusion. In the absence of clinical experience the experimental results suggest an increase in the LD50 of Gramoxone of 3 to 5 fold. This, if applicable to man would be very significant in accidental poisonings and in some cases of suicide. However, in the Japanese context, where volumes of Gramoxone in excess of 100 mls are often ingested it is possible that the emetic will not dramatically alter the number of fatalities. Consideration was also given to increasing the safety of Gramoxone by selling a more dilute solution (e.g. 5% paraquat ion). I believed this likely to be effective since
(1) it would increase the volume of Gramoxone that would be required to be ingested to cause death,
(2) it may enhance the action of emetic by increasing the volume of distribution of paraquat in the stomach and hence increase the amount of paraquat removed as a result of emesis.

ICI (J) did point out that it may take years to get registration for a dilute formulation of Gramoxone and there may be commercial problems with this approach.

Thursday 17 August (pm)

Those present: representatives from Takeida Chemicals and Nihon Nohyaku, Kamisan and Bill Riddell.

At this meeting I outlined the basis for our recommended treatment of paraquat poisoning and the likely advantages of incorporating an emetic into the formulation. This developed into a question and answer exercise in which their awareness of the limitations of treatment was exposed. Subsequently I had another meeting with representatives of these two companies on Monday 21 August (pm) at which the treatment of paraquat poisoning was discussed further.

Other Meetings

1. I met with Professor Y Kasuya, Department of Chemical Pharmacology, University of Tokyo, over lunch on Monday 21 August with Kamisan.

2. Met Professor H Kitagawa, (Department of Biochemical Pharmacology, Faculty of Pharmacology Sciences, University of Chiba) with Kamisan and Bill Riddell on Tuesday 2-4 pm. Professor Kitagawa is Chairman of the Classification of Poisonous Substances Committee, Ministry of Health and Welfare.

3. I met with Hiranga (Member of working group reporting to the Classification of Poisonous Substances Committee, Ministry of Health and Welfare) on Tuesday 4 pm.

At these meetings I discussed the problem of Gramoxone poisoning in Japan, the available treatment and ICI's attempts to make the formulation safer by the addition of an emetic. In no case did the toxicologists appear critical of either the product or ICI(J). They all recognised the difficulty in preventing a would-be suicide using Gramoxone and they agreed that if Gramoxone was not available another agent or method would probably be used. Since none of these toxicologists appeared hostile I concentrated on discussing the mechanism of toxicity and the recommended treatment regime. I must conclude that these toxicologists were being either disingenuous or they were not the source of criticism of Gramoxone.

Finally, on Wednesday 23 August (pm) I met with Kamishikiryosan and Takeisan to discuss the production of a booklet to be circulated to the Japanese medical community. This appeared a much more comprehensive document than the Guide to Treatment issued in the UK. It was agreed that CTL would see a copy of this document before it was circulated in Japan, and that I should send a copy of a recent review of the toxicity of paraquat which is at present 'in press' along with other references which might help in the production of a treatment booklet.

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