4P/1/19.

Dr G Teal
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LLS/JSA 188 7 August 80

Dear Godfrey,

Thank you for sending the preliminary results of Yanagita's study on the effect of PP796 on the toxicity of paraquat (GT/Hi 24 July).

While I am aware of the desirability to demonstrate the efficacy of PP796 in reducing the toxicity of paraquat in experimental animals, I believe there are several reasons why ICI (J) should not proceed with these studies.

Firstly, it appears that in the initial studies carried out at CTL the selection of dogs which did not vomit when given Gramoxone without emetic was critical. I accept that if this cannot be repeated in Japan, it is necessary to use another species. However, from the preliminary data in mini pigs that it appears they do not vomit when given paraquat alone there can be a very considerable delay before vomiting occurs when paraquat is given with PP796. This suggests that the mini pig may not be a good model for the situation in man. In humans Gramoxone often causes delayed vomiting. The addition of PP796 should make vomiting more certain and occur within a short time of ingestion.

Secondly, there is good evidence in man that PP796 is an effective emetic. Our experience with several species of experimental animal (now also mini pigs) indicate that higher doses of emetic are required to induce emesis than in man. The effectiveness of PP796 in reducing mortality is likely to be extremely difficult to prove statistically because the number of cases where lethal, but not massive, doses are encountered do not constitute a large percentage of the total number of suicide attempts.

However, I have enclosed for your interest copies of file notes I wrote concerning a recent case of paraquat poisoning involving emetic. Should the patient continue to make progress and survive I think he will be an excellent example of a survivor who consumed a lethal dose which was small enough for the emetic to be effective in saving his life.

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I must ask you not to use this information outside ICI at present. The patient still has considerable damage to his mouth and throat. We are hopeful that this case will be published by the clinicians involved so we shall be able to reference it to the relevant authorities.

Fourthly and finally, it is going to add to our problems if negative experimental data is produced in Japan. I do not think we would be contributing to an understanding of the usefulness of the emetic if negative data is generated in a species dissimilar to man.

It is, therefore, my considered opinion that it is not necessary for ICI (J) to proceed with Yanagita's studies. Should you, on balance, wish to continue with experimental studies, please let me know and I shall try to assist you in their design.

I hope all is well with you. Please give my regards to all.

With kind regards

Yours sincerely,

Dr Lewis L Smith