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CONFIDENTIAL

HUMAN DATA WITH THE PARAQUAT EMETIC (PP796)

I have reviewed the data presented on the phosphodiesterase inhibitor PP796 (ICI 63197) in ICI Pharmaceuticals Reports by Farrell, F.G. in 1970 (PH18987C) and Bayliss P.F C. in 1973 (PH 20992C). Clinical trials were performed on this drug in human volunteers as well as in patients with various diseases. It was identified during the course of these trials that a side-effect of the drug was nausea and vomiting in some individuals.

Following studies at CTL in dogs, pigs and monkeys it became clear that PP796 was an effective and reliable emetic agent of considerable potency. As a result, PP796 was chosen in January 1976 as a candidate for addition to the Paraquat concentrate Gramoxone.

It was clearly crucial that PP796 must be added to Gramoxone at an effective concentration in a minimally lethal dose of Paraquat. A report by Dr M.S. Rose (CTL/R/390R) presented a summary of some of the clinical data from the above reports where he gave evidence to support such a concentration. It was suggested that a concentration of 0.05% w.v. (or 5mg in 10ml) PP796 should cause emesis in man within one hour following ingestion of a minimal lethal dose of Gramoxone in the majority of poisoning cases.

I would like to point out that the human data presented in Report CTL/R/390(R) is very misleading. In the attached table, I have presented two sets of data. Data presented by Rose in CTL/R/390(R) is shown at the top. The actual data presented by Bayliss in PH20992C is shown at the bottom.

There are three important differences between the data from CTL/R/390(R) and PH20992C.

1. Data from 2 volunteers dosed with 3mg PP796 has been omitted.

2. Data showing a 4/37 vomit response (from patients with various diseases) at 2mg PP796 has replaced a 0/3 response in the volunteer study on which the rest of the data is based. (Incidentally 4/37 should be 4/1356 dosings or 0.3%.

3. Time to vomit at the top dose of 8mg PP796 which was 2 hours has been completely ignored, yet the author stresses how important it is that emesis occurs within 30 min.

Prediction of a likely ED50 from the human data is obviously very difficult with small group sizes. However, much is known in animals about the steepness of the dose versus onset of emesis curve with the emetic. By normalising "selected data" the percentage vomiting response of 0,11,50,100 following 1,2,4 and 8mg PP796 produces a plausible dose-response relationship. Consequently,this infers that "a dose of 5mg, PP796 in a minimally lethal dose of Paraquat would probably cause emesis in the majority of cases" as suggested by Rose.

However, on examination of the full data there is no such dose response. The minimal effects observed at 4 and 8mg PP796 suggest that 4-8mg doses are probably nearer threshold in man not maximal. Furthermore, the dose response curves in pig, dog and monkey are all very similar across the same dose range. I would suggest that the emetic dose response curve of PP796 in man is similar to these other species. Thus, I disagree with the conclusions in report CTL/R/390 (R), which suggest that the emetic is 10 times more potent in man.

As toxicologists, we are continuously asked to make scientific judgements of risk assessment issues using experimental responses in different species to particular chemicals. In the case of Paraquat and PP796 we are in a unique position of being able to judge responses in man with both chemicals with a good deal of confidence. It appears to me that the above case for choosing an effective emetic dose in Paraquat has not been judged correctly. As far as I am aware (after studying the emetic correspondence files) the human data with PP796 was not questioned during the period 1976/77. Consequently the human dose response data with PP796, reported by Rose, has remained to this day undisputed.

I have documented my findings in this letter since I feel that this issue is extremely important in the impending ICI Agrochemicals Board Paper which is to discuss increasing the level of emetic in Gramoxone. I am fully aware that a 5 fold increase in emetic concentration was recommended in 1985. This followed further observations in the dog with Paraquat and PP796. Our current studies in 1990 are in very close agreement. Thus, the effective dose of PP796 in dogs to produce emesis within 30 minutes is about 0.2mg/kg. Therefore, if man were to respond to the emetic at similar dose levels as the dog, then a minimal lethal dose of Gramoxone (10ml) should contain at least 15mg PP796 or three times the 1976 proposed level.

The whole argument is based on whether or not there are species differences in response to PP796. I think it is extremely unlikely that PP796 is ten times more potent in man compared to pig, monkey and dog as stated by Rose, having reviewed all the data at my disposal.

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Emetic Action of PP796 in Man

Data from Table 1 (CTL/R/390)

mg	mg/kg	n	Nos vomiting	% vomiting response
1	0.015	2	0	0
2	0.03	37	4	11
4	0.06	2	1	50
8	0.11	1	1	100

Complete Data from Clinical Report PH20992

mg	mg/kg	n	Nos vomiting	% vomiting response
0.25	0.0035	1	0	0
0.5	0.007	1	0	0
1	0.015	2	0	0
2	0.03	3	0	0
3	0.04	2	0	0
4	0.06	2	1 (at 30min)	50
8	0.11	1	1 (at 2hr)	100