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721.01 paraquat

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Your ref	Our ref	Tel ext	Date
	DMF/DMH	391	19 October 1976

Dear Nils

Please find enclosed a draft copy of an appraisal of the emetic potential of PP796 with particular reference to the proposed concentration for use in paraquat formulations.

To expedite transmission to yourself a copy is, in addition, being sent via Infotec to your Richmond office for subsequent relay. If all goes smoothly this copy should reach you first.

When you have considered this document I would like to support the suggestion that Dr Cavalli acquaint himself directly with the basis of our proposed concept by meeting the appropriate members of Pharmaceuticals Division. In addition, our ideas on the environmental aspects of PP796 are crystallising and we could benefit from a discussion on this topic.

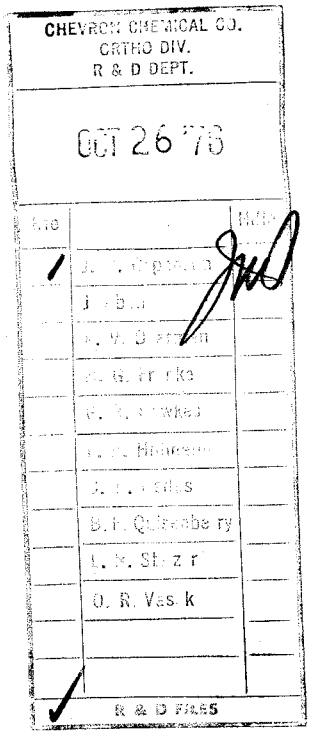
I look forward to your comments.

Yours sincerely

D. M. Harrison

P.P. D M FOULKES

Encs.



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THE QUEEN'S AWARD TO INDUSTRY 1967 1970 1973 1974

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REPORT NO: CTL/R/300

THE CONCENTRATION OF PP 796 REQUIRED TO PRODUCE EMESIS IN EXPERIMENTAL ANIMALS AND AN ESTIMATION OF THE EMETIC DOSE IN MAN.

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Summary

From information following clinical trials and data from experimental animals, it is concluded that PP 796 should be added to paraquat formulations at a level of 5 mg in 10 ml (0.05%). It is estimated that about 70% of those ingesting 10 ml of this formulation will vomit within an hour.

Introduction

The ICI development compound ICI 63197 produced by ICI Pharmaceuticals Division is a phosphodiesterase inhibitor (Farrell, 1970, Vol II) which has been shown to have a potent emetic action (Bayliss, 1973). This compound has been reclassified by ICI Plant Protection Division as PP 796.

PP 796 is included in a paraquat formulation in amounts that will cause emesis within 1 hour in dogs and monkeys, the toxicity of the formulation to these species is reduced (Rose, 1976). In order to reduce the toxicity of the paraquat formulation to man, therefore, it will be necessary to add sufficient PP 796 to cause emesis, in a volume of paraquat concentrate that would normally be lethal if ingested. A volume of 10 ml of the 20% w/v paraquat concentrate is considered to be the smallest volume containing a possible lethal amount of paraquat to man (Fletcher, 1974). The question that remains to be answered therefore, is what amount of PP 796 should be added to this volume of formulation?

An emetic response in dogs, monkeys and pigs has been obtained with PP 796 over the dose range 0.1-1.0 mg/kg body weight (Table 1). On this basis a dose of 2 mg/kg was chosen as one that would clearly ensure vomiting in dogs and monkeys, and this dose was, therefore, used for studying the effect of emesis on paraquat toxicity in these species (Rose, 1976).

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Studies in dogs using intravenous infusion have suggested that the emetic effect may be a response to the rate of increase in plasma concentration of PP 796 rather than due to a critical plasma concentration being reached (Hepworth, 1971). Certainly, the relationship between dose and emetic effect is steep (Table 1).

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Clinical studies (Bayliss, 1973) have indicated that man is more sensitive to the emetic effects of PP 796 than the experimental animals studied, emesis being seen with doses in the range 0.03-0.11 mg of PP 796/kg body weight(equivalent to total doses in the range 2.8 mg). Healthy volunteers (average body weight 70 kg), 1 was given 0.25 mg, 1 was given 0.5 mg, 2 were given 1.0 mg, 3 were given 2 mg, were given 3 mg, 2 were given 4 mg and one was given 8 mg. Of these, the volunteer given 8 mg vomited as did one of those given 4 mg. Nausea was a marked effect reported by almost all of the volunteers. It can be seen that when the blood levels of PP 796 in the 2 volunteers given 4 mg are compared, the one that vomited absorbed the compound more quickly than the other (Table 2). This suggests that, as with dogs, the rate of absorption might be critical in determining whether vomiting will occur. After this first volunteer study, one conclusion reached was that "The agent was poorly tolerated at doses above 1-2 mg. Nausea, vomiting, dizziness, sweating and flushing were complained of". As a consequent of this, all further studies were carried out with a maximum dose of 2 mg. Of those who took 2 mg, approximately 10% vomited and 60% complained of nausea.

From the limited data available in man, therefore, it can be argued that a dose of 5 mg should certainly cause nausea and ought to induce vomiting in approximately 70% of those ingesting it (Table 1). It should be noted that the clinical studies were carried out using PP 796 in tablet form. They will have

lead to an inevitable delay in absorption (Farrell, 1970, Vol. I). When present in paraquat formulations PP 796 will be in solution and this much more readily absorbed. An additional factor that should also be considered is the irritancy of the paraquat concentrate, which causes nausea and vomiting (albeit after a delay of many hours).

In conclusion, the addition of PP 796 to formulated paraquat at the rate of 0.05%(5 mg emetic to 10 ml formulation) should be sufficient to ensure that most people ingesting 10 ml will vomit. Inspection of the statistics of paraquat poisoning incidents reported to ICI shows that most cases involve ingestion of quantities in excess of 20 ml, many suicides involving 50 ml or more. Under these circumstances, and considering 1) irritant nature of the formulation, and 2) the fact that PP 796 will be in a soluble, dispersed form, it seems highly likely that vomiting will occur within an hour, with a consequent reduction in the amount of paraquat available for absorption.

MSR:SDL
18 Oct '76

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TABLE 1

The emetic action of PP 796

	Dose	Nos. Vomiting	% Vomiting response	Total dose (mg)
Dog*	0.5 mg/kg	3/8	35	
	1.5 mg/kg	6/8	75	
Pig**	0.25 mg/kg	0/8	0	
	0.5 mg/kg	3/8	35	
	1.0 mg/kg	5/8	63	
Monkey+	0.1 mg/kg	4/19	21	
	0.2 mg/kg	6/16	38	
	0.5 mg/kg	4/5	80	
Man++	0.015 mg/kg	0/2	0	1
	0.03 mg/kg	4/47	11	2
	0.06 mg/kg	1/2	50	4
	0.11 mg/kg	1/1	100	8

* Data from Farrell (1970) Vol. II.
** Data from Broome (1972)
\+ Data from Davies and Hepworth (1969)
++ Data from Bayliss (1973)

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TABLE 2

+Comparison of blood values of PP 796 in 2 volunteers given 4 mgs in tablet form

	micrograms PP 796/ml		
Hours after dosing	1	2	3
Volunteer No 10*	0.081	0.041	0.034
Volunteer No 11	0.045	0.056	0.044

* Vomited after 30 minutes

+ Data from Bayliss (1973)

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References

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Davies, G. E. & Hepworth, W (1969) — Emetic effects (of 63,197) in monkeys and marmosets. Report No: CPR095/14

Farrell, F. G. (1970) — ICI 63,197 Submission of evidence to the Committee on Safety of Drugs (Vol. I Chemistry and Pharmacy; Vol. II Pharmacology and Biochemistry; Vol. III Toxicity and Proposed Clinical Trials). Report No: PH18987C

Fletcher, K. (1974) — in Forensic Toxicology, ed. by B. Ballantyne, published by John Wright and Sons Ltd., Bristol.

Hepworth, W. (1971) — Infusion studies on emetic effects (of 63,197). Report No: CPR095/20 168A

Rose, M. S. (1976) — The effect of administration of an emetic (PP 796) on paraquat toxicity in dog and monkey. Report NO: CTL/R/391 (in preparation)

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