IMPERIAL CHEMICAL INDUSTRIES
Plant Protection Division
Fernhurst Haslemere Surrey
England

DOSSIER NO: C1.2/03

RIC4220

PP 796

A POTENT EMETIC

RDW
ZB 40

7 4 78

INTRODUCTION

It was developed initially as a drug for the relief of asthma. Toxicological results were presented to the U.K Committee for the Safety of Medicines who then granted a Clinical Trials Certificate. The trials showed that PP796 could not be used therapeutically because it was an emetic agent of considerable potency. Because PP796 is such an effective emetic only small, toxicologically insignificant, quantities of it are required in 'Gramoxone' formulations.

PP796 is the code name for 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one.

EMETIC ACTION

That PP796 is a highly potent emetic agent has been demonstrated in tests with a variety of species, including man.

Pigs

Groups of 8 pigs were fed twice/day for two days diets containing 4, 10, 20 and 40 g PP796/long ton. These rates were chosen to give 0.1-1.0 mg/kg to 20 kg pigs. They were observed for emesis and food eaten and results were as follows:

Dosage level		Number of Pigs	Response after 2 feeds			% Emeses
Concentration in diet	mg/kg/pig		Refused diet	Emesis	Slow eating	
40 g/ton	1.0	8	8	5	-	62
20 g/ton	0.5	8	8	3	-	37.5
10 g/ton	0.25	8	6	0	2	-
4 g/ton	0.1	8	0	0	8	-

Monkeys and Marmosets

Seven monkeys and 2 marmosets were dosed via a stomach tube with 0.025-1.0 mg pp796/kg on various occasions. The results obtained in summary were:

Dose (mg/kg oral)	Number of administrations	Number of emeses	% emeses
0.025	6	2	33
0.05	5	0	0
0.1	24	5	21
0.2	19	8	42
0.3	15	2	13
0.4	15	5	33
0.5	5	4	80
0.6	2	2	100
1.0	2	2	100

The speed with which the animals were sick depended on the dose but at amounts of 0.6 mg/kg this occurred within 10-30 minutes.

In a further series of tests monkeys were given a mixture of 'Gramoxone' and PP796 at a rate of 100 mg paraquat plus 2 mg PP796/kg. Most (6/8) of the animals vomited within an hour and those which did survived an otherwise lethal dose of paraquat. The toxicity to monkeys of 'Gramoxone' formulation in the presence of an emetic dose of PP796 was estimated to be lowered by a factor of approximately 5.

Dogs

Four groups each of 8 Beagle dogs were dosed daily with capsules containing 0, 0.15, 0.5 or 1.5 mg PP796/kg. Vomiting occurred in six of the eight animals on the highest dose and in three of those receiving 0.5 mg/kg.

When dogs were given sufficient 'Gramoxone' to provide a dose of 20 or 30 mg paraquat/kg none vomited and 3/4 died. However when either 2 mg or 3 mg PP796/kg was added to the 'Gramoxone' all dogs dosed vomited within 1 hour and all survived.

Man

Clinical studies have indicated that man is more sensitive to the emetic effects of PP796 than the experimental species studied, emesis being seen with doses in the range of 0.03-0.11 mg PP796/kg (equivalent to 2-8 mg per 70 kg man). 12 healthy volunteers were given 0.25-8 mg. The man given 8 mg and one of the two given 4 mg vomited and most reported nausea and many dizziness, sweating and flushing. All of these symptoms would provide warning if 'Gramoxone' containing PP796 were swallowed by mistake. In further tests when a maximum of 2 mg PP796 was taken vomiting and nausea resulted. From these results it is concluded that a dose of 5 mg PP796 is likely to cause vomiting in the majority of those ingesting it.

Statistics of paraquat poisoning incidents indicate that most of those involved ingested in excess of 20 ml 'Gramoxone'. Inclusion of 5 mg PP796 in 10 ml of 'Gramoxone' is therefore likely to cause vomiting in the majority of those ingesting this quantity or above. This would have the effect of reducing the amount of paraquat available for absorption from the stomach and greatly increasing the recovery rate following accidents.

EFFECTS ON MAN

The UK authorities granted permission for the use of PP796 in clinical trials on man as a treatment for asthma. In the trials it showed no consistent effect upon blood pressure of either normotensive or hypertensive subjects, no beneficial effect on bodyweight in obesity and no effect on thyroid, or adreno-cortical function.

The effects of dosing with PP796 were nausea, vomiting and dizziness at 1 mg unit doses and above. Agina pectoris appeared in two subjects following chronic dosing of 2 mg and above after four and six weeks respectively. The effects ceased on cessation of dosing. Capillary fragility with a positive Hess's Test was seen in one subject. The half-life of PP796 in man was between 1½ and 3½ hours.

In trials in the UK, farmers applying 'Gramoxone' with and without PP796 were unable to detect any differences between the two formulations in effectiveness, ease of handling or any other parameter.