

IMPERIAL CHEMICAL INDUSTRIES LIMITED
Central Toxicology Laboratory

RIC4206

The Effect of PP796 on Paraquat Toxicity

Summary

PP796 is a potent inhibitor of gastric emptying as well as being a potent oral emetic. Its action on gastric emptying has been demonstrated even at sub-emetic doses in monkeys.

These two properties combined (inhibition of gastric emptying and emesis) result in a very significant reduction in the plasma paraquat concentration over the first 5 to 10 hours in experimental animals given mixtures of paraquat and PP796. Since the plasma paraquat concentration is critical in determining the lung concentration of paraquat and thus the severity of poisoning in human cases, the inclusion of PP796 in paraquat formulations should have a marked effect in reducing the toxicity.

Effect of PP796 as an emetic

PP796 is a novel oral emetic, active at extremely low doses and causing vomiting in experimental animals, such as the dog and monkey, within an hour and often within 10 to 20 minutes after dosing (Rose 1976; Rose *et al* 1976). It is a "centrally" acting emetic and does not cause vomiting through a local irritant effect on the stomach.

Effect of PP796 on gastric emptying

PP796 has been shown to inhibit gastric emptying in the mouse, rat and monkey (Table 1). The mouse and rat lack the ability to vomit and the effects on gastric emptying were therefore measured using doses which will cause vomiting in species like the dog or monkey. The inhibition of gastric emptying seen in monkeys was striking even though it was obtained using a relatively low, sub-emetic dose.

The effect of PP796 on the absorption of paraquat into the blood

In rats, the administration of PP796 together with paraquat significantly retards the appearance of paraquat in the blood (plasma), and eliminates the early high peak seen in the first hour (Fig. 1). This effect is due to inhibition of gastric emptying since no vomiting occurs in rats. This shows that paraquat is not readily absorbed from the stomach.

When PP796 and paraquat are given to dogs and monkeys, as well as inhibition of gastric emptying, vomiting also occurs and the blood level of paraquat is very markedly reduced (Fig's 2 and 3).

The relationship between the concentration of paraquat in blood and survival in cases of paraquat poisoning

The discovery that lung actively accumulates paraquat from the plasma (Rose et al, 1974; Rose et al, 1976) led to the recognition that the concentration of paraquat in plasma would determine the concentration in the lung, and thus the severity of poisoning. An analysis of the relationship between the concentration of paraquat present in plasma and mortality shows that those patients with blood levels above a critical value (approximately 0.3 micrograms/ml, 24 hours after poisoning) have died. It is clear, therefore, that the survival of people who accidentally or deliberately ingest paraquat will be dependant on the concentration of paraquat achieved in the blood during the first 24 hours following ingestion. The inclusion of PP796 in the paraquat formulation should lead to a considerable reduction in the plasma paraquat, as demonstrated in dogs and monkeys (Fig's 2 and 3), and should make the formulation much less toxic.

References

Rose M S, Parkinson G R and Laird W J D (1976); Report No. CTL/R/391

Rose M S (1976); Report No. CTL/R/390(R)

Rose M S, Smith L L and Wyatt I (1974); Nature 256 314-315

Rose M S, Lock E A, Smith L L and Wyatt I (1976) Biochem Pharmacol 25 419-423

Michael S Rose (Dr)

MSR/JFM/10 Aug 78

TABLE 1

Effect of PP796 on Gastric Emptying

Animals were starved for 24 hours and then dosed orally with either phenol red or ^{51}Cr in the presence or absence of PP796 (given orally or by subcutaneous injection). The animals were killed after 1 hour and the amount of phenol red or ^{51}Cr remaining in the stomach was measured.

MOUSE (non-vomiting species)

% remaining in stomach

Control	3.9 ± 0.7
oral PP796 2.5 mg/kg	44.8 ± 4.6
s.c. PP796 1.0 mg/kg	49.4 ± 4.4

RAT (non-vomiting species)

% remaining in stomach

Control	16.2 ± 1.8
oral PP796 1.0 mg/kg	58.5 ± 7.3
s.c. PP796 1.0 mg/kg	71.1 ± 7.6

MONKEY* (vomiting species)

% remaining in stomach

Control	33.7 ± 7.4
oral PP796 0.2 mg/kg	85.7 ± 5.4

* Dose of PP796 used was $\frac{1}{10}$ th of the emetic dose and did not cause vomiting in any of the animals.

FIGURE 1 THE EFFECT OF PP796 ON PLASMA PARAQUAT CONCENTRATION IN RATS

PQ dosed orally at 126 mg/kg
with or without PP796 at
1 mg/kg.

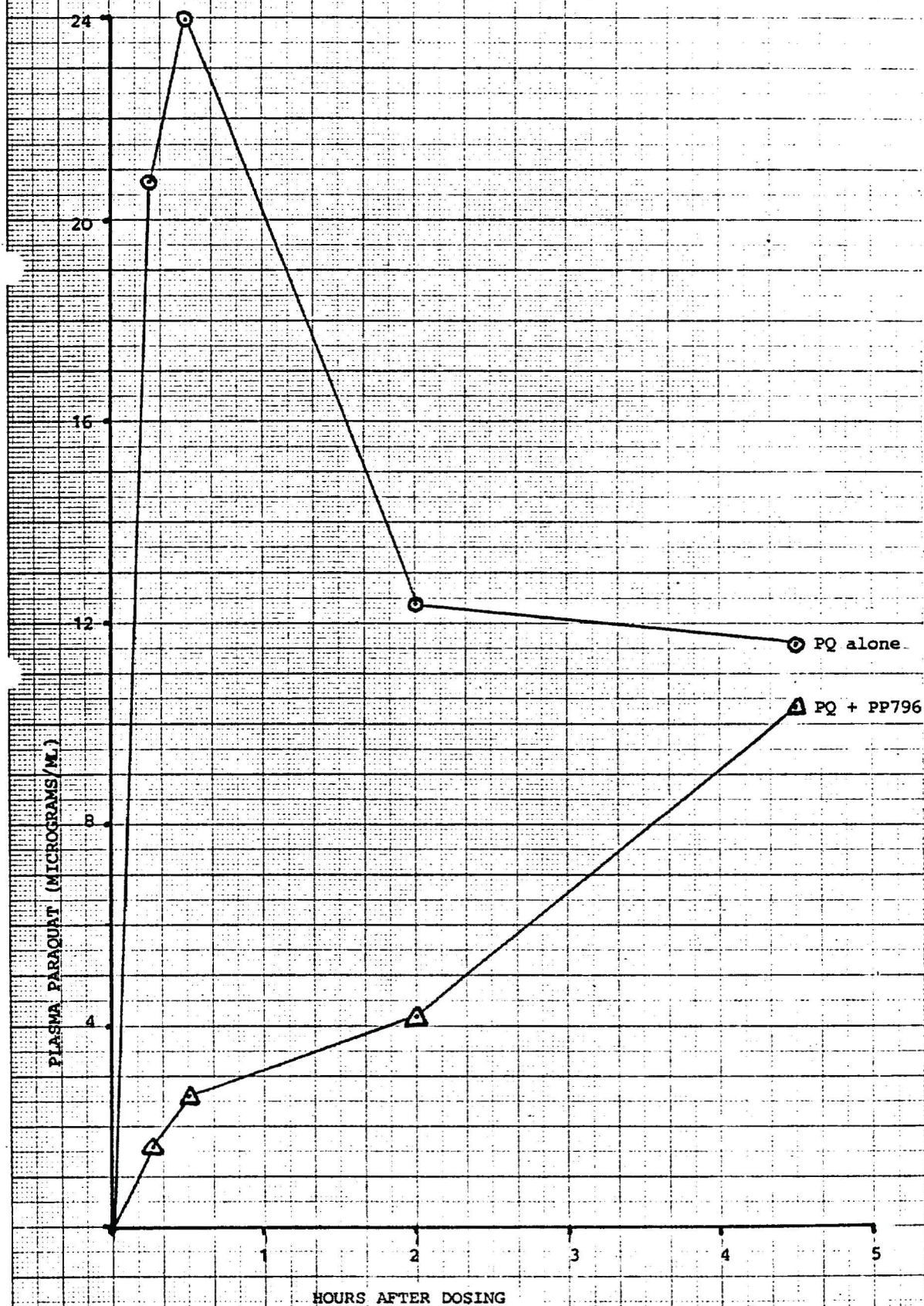


FIGURE 2

THE EFFECT OF PP796 ON PLASMA PARAQUAT CONCENTRATION IN DOGS

PQ dosed orally at 30 mg/kg
with or without PP796 at
3 mg/kg

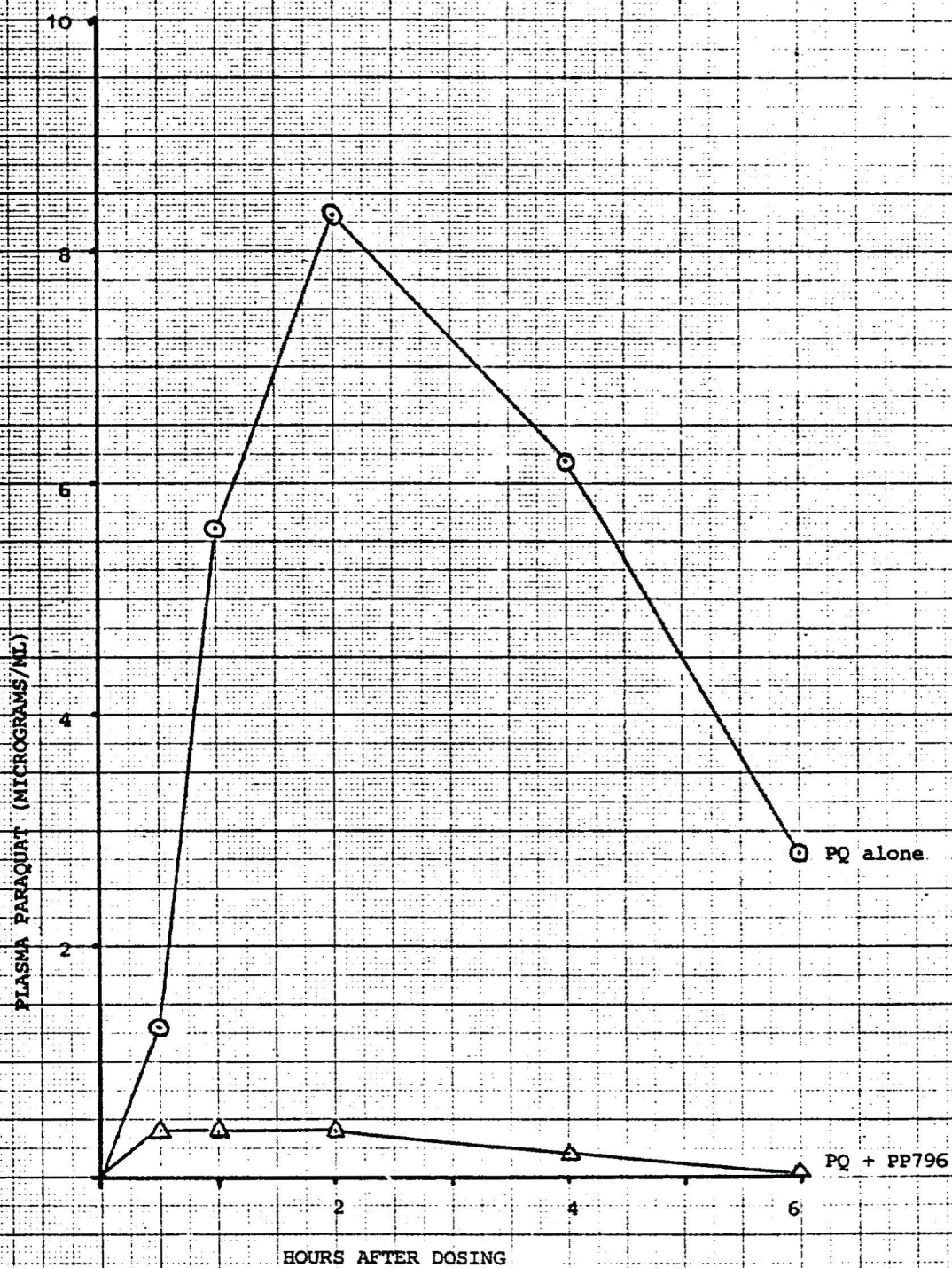
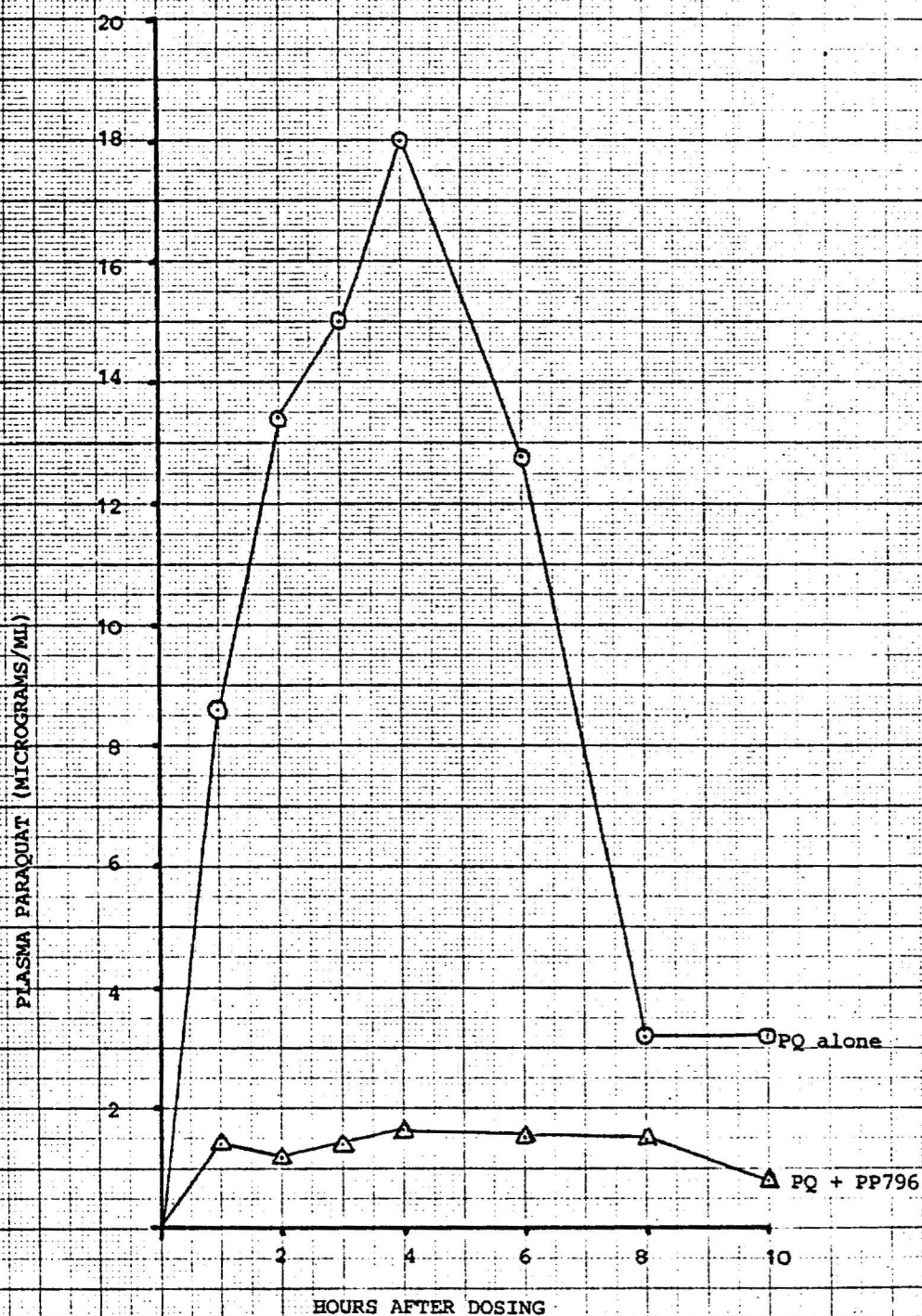


FIGURE 3 THE EFFECT OF PP796 ON PLASMA PARAQUAT CONCENTRATION
IN MONKEYS

PQ dosed orally at 100 mg/kg
with or without PP796 at
2 mg/kg



THE CONCENTRATION OF PARAQUAT IN THE PLASMA OF PATIENTS FOLLOWING THE INGESTION OF PARAQUAT

