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Emetic data

Your ref	Our ref	Telex	Date
	MSR:SDL	179	14 June 76

TOXICOLOGICAL ASSESSMENT OF EFFICACY OF PARAQUAT EMETIC FORMULATION
- PRELIMINARY REPORT

Three studies are in progress, in dogs (CTL) rats (CTL) and monkeys (Huntingdon Research Centre).

The studies in dogs and monkeys have been set up to answer the questions 1) is the emetic effective in causing vomiting in the presence of a vast excess of paraquat? and 2) does the emetic action alter the toxicity of paraquat?

The study in rats was set up to answer the questions 1) does paraquat interfere with the absorption of the emetic? 2) does the emetic interfere with the absorption of paraquat? The rat was chosen for this study as it does not vomit and any effect must, therefore, be due to pharmacokinetics.

Preliminary results

Monkeys

Four monkeys were dosed with Gramoxone at 100 mg paraquat ion/kg body weight. All animals died within 3-4 days. Four monkeys were dosed with the same amount of Gramoxone plus emetic (at 2 mg/kg body weight). All four animals vomited, two about 20 minutes after dosing, 1 after approximately 45 minutes, and 1 not for approximately 8 hours. The three animals that vomited early survived but the animal that vomited later died a delayed death from pulmonary damage.

The concentration of paraquat in the plasma of both groups of animals is shown in Figure 1. The emetic group have clearly very much less paraquat than those animals given Gramoxone W. Even the animal which vomited very late had very low plasma paraquat levels over the first 10 hours. This may be a consequence of an effect of the emetic on gastric emptying (see note on discussions with Hammersmith Group, MSR:SDL, 11 May 76). The experiment will be repeated.

Dogs

Four dogs were dosed with 20 mg paraquat cation/kg as Gramoxone W. Three of the animals died in the first week of poisoning.

Four dogs were dosed with the same amount of Gramoxone plus emetic (2 mg/kg body weight). All four animals vomited within 15 minutes. All four animals survived.

The concentration of paraquat in the plasma of these two groups of animals is shown in Figure 2. Again the emetic group have very much less paraquat in their plasma.

The experiment will be repeated using 30 mg paraquat/kg and 3 mg/kg emetic (ie the same formulation at a higher dose level).

Rats

Groups of rats were dosed orally with 126 mg paraquat cation/kg, with this dose of paraquat plus 1 mg/kg of emetic orally and with 1 mg/kg emetic alone. Rats were killed at 15 and 30 minutes after dosing and the plasma concentration of paraquat, and emetic measured, and the amount of paraquat in the lung measured. Table I shows that at both 15 and 30 minutes, the presence of emetic has profoundly lowered the paraquat in the plasma to 8% and 11% of those animals dosed with paraquat alone. The lung concentration of paraquat is also reduced.

Paraquat has no significant effect on the plasma concentration of the emetic.

The most likely explanation of these results is that the emetic slows gastric emptying.

Further experiments killing animals at later times are in progress.

Summary

- 1) The emetic action of R50796 in dogs and monkeys is unaffected by paraquat.
- 2) When vomiting occurs within an hour, animals survive an otherwise lethal dose of paraquat.
- 3) R50796 may slow gastric emptying, an effect which will have several important beneficial implications:
 - a) if vomiting does not occur, there will be much more time for treatment to be applied and therefore be effective.
 - b) If large amounts of Gramoxone are swallowed deliberately, if vomiting still leaves significant amounts of paraquat in the stomach, absorption will be slow and thus more time available for treatment.

Conclusions

On the preliminary results, I believe there will be no toxicological problems associated with the formulation. Moreover, it appears that the idea of a safer formulation based on addition of an emetic "works".

Further work

Apart from repeating the above experiments, several other experiments should be carried out.

- 1) LD50 of the emetic formulation in monkeys
- 2) LD50 of the emetic formulation in rats

TABLE 1

Effect of PQ and emetic on PQ and emetic absorption
in rats

PQ dosed orally at 126 mg cation/kg

Emetic dosed orally at 1 mg/kg

		<u>PQ conc (nmoles/g or ml)</u>			
		<u>Plasma</u>		<u>Lung</u>	
15'	PQ alone	20.9	+ 9.1 (5)	7.3	+ 3.5 (5)
	PQ+emetic	1.6	+ 0.9 (5)	1.9	+ 0.5 (5)
30'	PQ alone	23.9	+ 8.4 (5)	7.4	+ 2.9 (5)
	PQ+emetic	2.6	+ 1.3 (5)	2.1	+ 1.3 (5)

		<u>Emetic conc (nmoles/ml)</u>	
15'	Emetic alone	0.92	+ 0.42 (5)
	Emetic + PQ	0.65	+ 0.36 (5)
30'	Emetic alone	0.68	+ 0.29 (5)
	Emetic + PQ	0.53	+ 0.14 (5)

MONKEYS : Q IN PLASMA 100mg / Kg body wt.

EMETIC 2mcg / Kg body wt.

Plasma concentration
(micrograms/ml)

20

16

12

8

4

GRANOXONE ALONE

GRANOXONE + EMETIC

TIME AFTER DOSE (HR)

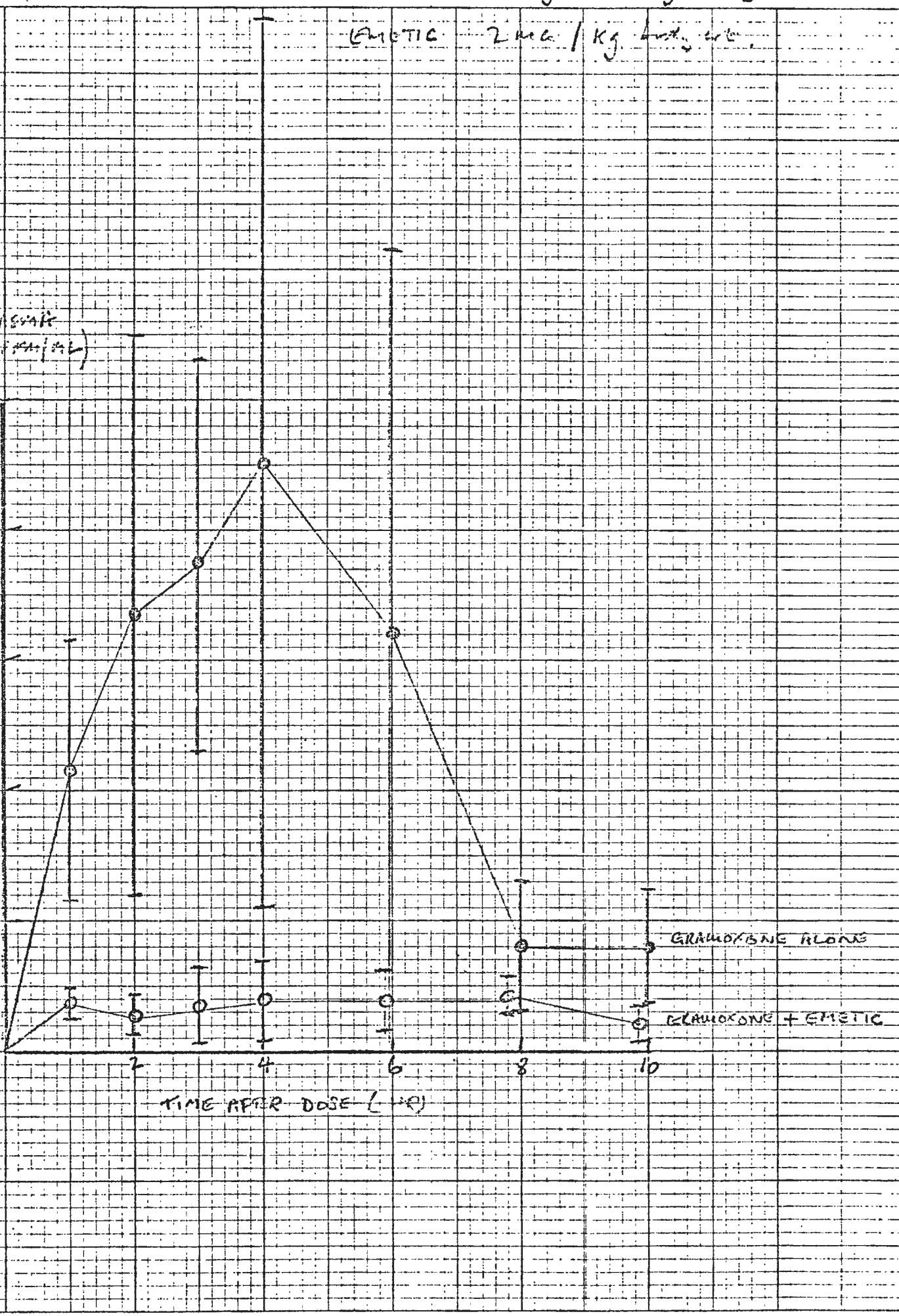
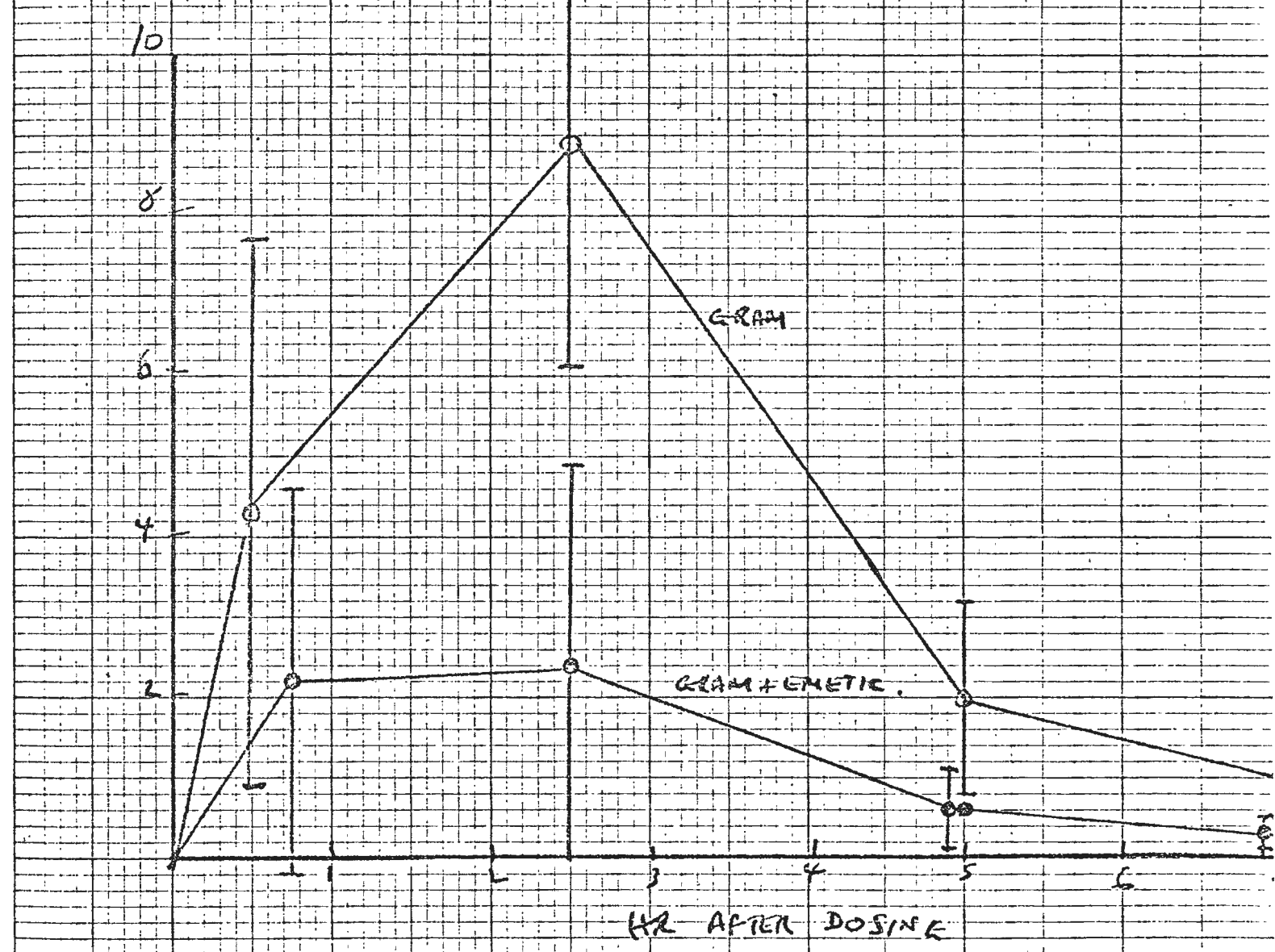


Fig 2.

DOG. Dose: 20 mg. curia / Kg. in Complan.

PO (g/ml plasma.)



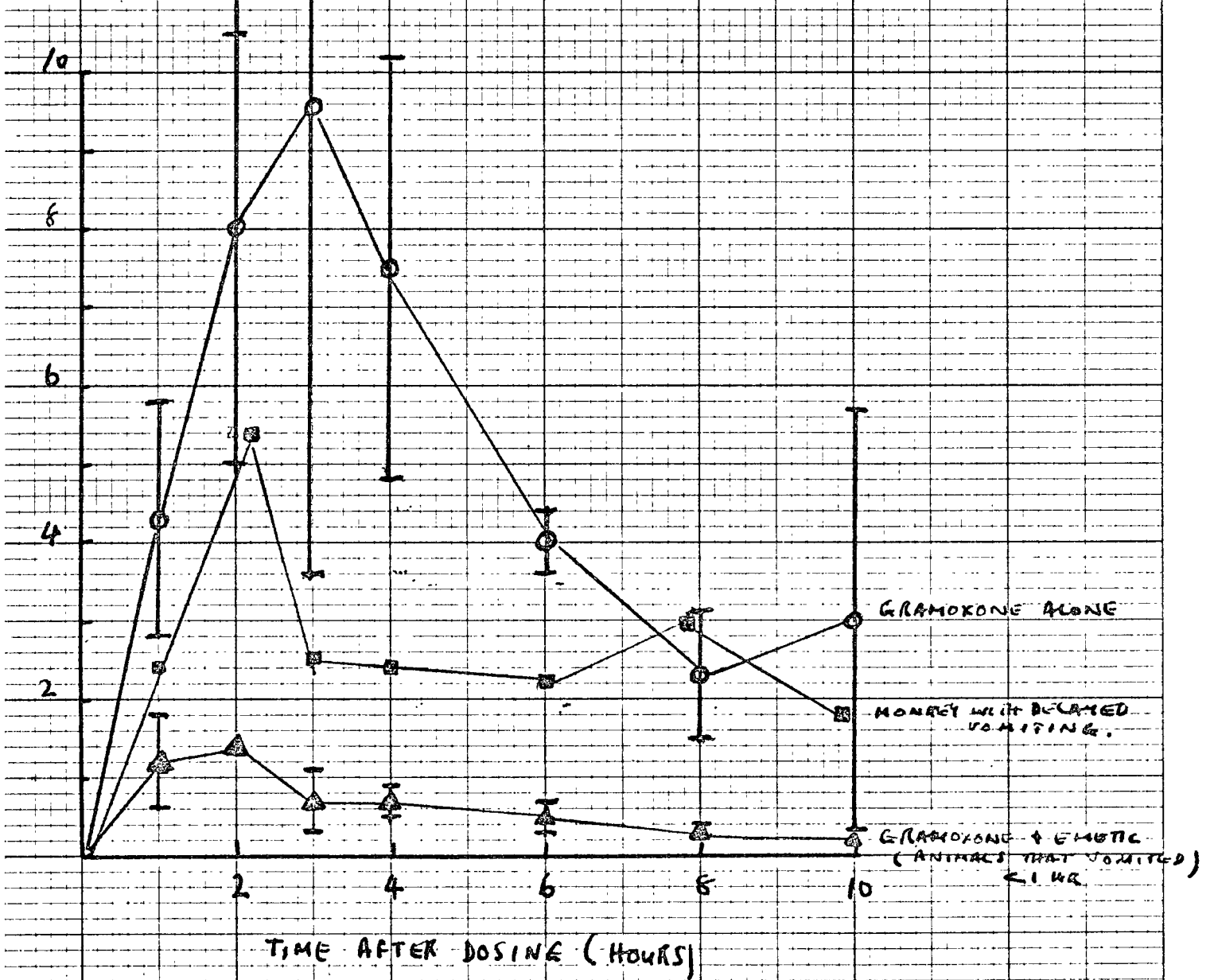
1. PG. PG. curia dogs to good health
 2. PG. PG. curia dogs dead after 4-5 days. 1 of the remaining will be with PG 27

EXPT 2.

MONKEYS : PO IN PLASMA

GRAMOXONE 100 mg PQ²⁴/Kg
EMETIC 2 mg /Kg.

mcGRAMS/ml PLASMA



EXPT 2. DOG : PA IN PLASMA

GRAMOXONE 30mg PO²⁴/kg
EMGITC 3mg/kg

