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PP796 : PARAQUAT

I have been asked by Peter Bramley to provide you with the evidence which has led CTL to recommend that the level of PP796 in some paraquat formulations be increased. This increase was suggested in order to evaluate its effectiveness in reducing the mortality in cases of human paraquat poisoning. I should like to emphasise that I have not claimed that increasing the concentration of PP796 will reduce the number of fatal paraquat poisonings, rather that the evidence from our experiments justifies an attempt to evaluate the effect in man.

Before PP796 was added to formulations of paraquat in the late 1970s several animal studies were carried out. In dogs, it was found that when paraquat and 2 mg PP796/kg PP796 were given to dogs at the same time the LD50 of paraquat was increased by a factor of approximately five. Similar studies were carried out in monkeys where the reduction in toxicity was found to be in the region of three-fold.

When it came to deciding the concentration of PP796 in 'Gramoxone' it was decided that the minimal lethal dose of formulation should contain a dose of PP796 likely to cause emesis. This dose was set at 5 mg/person based on the response in a few humans who had been given PP796 when it was under development at Pharmaceutical Division as an anti-asthmatic drug. Thus, the inclusion rate in 'Gramoxone' became 5 mg/10 ml of 'Gramoxone' (the minimal lethal dose). When this decision was made, it was thought that the clinician had many hours to remove paraquat from the stomach and lower intestine before lethal amounts of paraquat were absorbed into the plasma and accumulated in the lung. It is now clear from the data at CTL (and elsewhere) that the peak concentration of paraquat in the blood is reached within 1-3 hours and that the majority of the paraquat that is absorbed will be present in the blood within a few hours of ingestion. Therefore to be effective in reducing the toxicity of swallowed paraquat, not only must PP796 cause effective emesis, it must do so within a very short period of time. There seems little doubt that, at the present inclusion rate, PP796 is an effective emetic but there is no evidence that a significant percentage of paraquat poisoned patients vomit within 10 minutes of ingestion. It can be seen from the attached draft reports that it is necessary to induce vomiting very shortly after swallowing paraquat in order to maximise the reduction in the absorption of paraquat. These studies show that:

1. The amount of emetic given to dogs alters the time to vomiting. 0.1 mg/kg PP796 does not cause vomiting whereas 0.5 mg/kg causes vomiting within 30' and 3.0 mg/kg or greater causes vomiting within 10'.

2. Doses of 20 mg/kg PP796 appear to be super maximal and may cause harm to the dogs.

3. When a fixed dose of paraquat (20 mg/kg) is given to dogs along with various doses of PP796 it was found that 0.5 mg/kg PP796 reduced the absorption of paraquat by approximately 10-fold and 3 mg/kg or 20 mg/kg by approximately 50-fold.

As far as I can tell these are the first dose response curves which have been established in dogs for the effect of varying the dose of PP796, on its emetic activity or on its ability to alter the absorption of paraquat.

These data lead to the simple conclusion that after swallowing paraquat, the more rapid and effective is the vomiting the less absorption of bipyridyl will occur and consequently the toxicity will be reduced.

The data in man does not indicate that generally PP796 causes rapid vomiting within a few minutes. In some cases where vomiting has been reported very rapidly after swallowing and emesis is sustained, the patients have swallowed large amounts of formulation. In these cases large doses of PP796 have been taken which induces rapid emesis. However, large amounts of paraquat have also been consumed (this can approach x10 or x15 the LD50 of paraquat), in which case it is very unlikely that even rapid emesis will prevent a lethal dose of paraquat being absorbed.

In the context of Japan the following approximations can be made.

If we assume (1) average bodyweight of Japanese to be 50 kg
(2) the LD50 dose is 20 ml 'Gramoxone' (contains 20 mg PP796)
(NB. TBH has estimated LD50 to be 15 ml 'Gramoxone')

then dose level of emetic in an LD50 dose of paraquat is 0.2 mg PP796/kg.

This is well short of the optimum range of emetic in the dog studies which lies between 0.5 mg/kg and 3 mg/kg.

Assuming the formulation of paraquat is diluted from 20% paraquat cation to 4.5% paraquat cation and 4.5% diquat cation ('Preglox' L) and that the contribution of diquat to the toxicity of the formulation is minimal then a lethal dose of 'Preglox' L will be in the range of 40 to 80 ml. By increasing the dose of emetic to 40 mg in 40 ml (0.1%) then the dose of emetic for one mouthful (~40 ml) will be approaching 1 mg/kg (ie in the range of that which is optimal in the dog. There will also be the important additional advantage in that dilution will increase the volume of formulation that contains a lethal dose. This means that if emesis occurs and only 50% of the stomach contents are removed it is less likely that a lethal quantity of paraquat will remain in the stomach (cf if 40 ml of 'Gramoxone' is swallowed and 20 ml vomited a lethal dose may well remain).

The combination of the data from the dog studies, together with our understanding of the absorption of paraquat in man and the current profile of emesis in paraquat poisoned patients leads me to the conclusion that it would be sensible to add <u>at least</u> 0.1% PP796 to the 'Preglox' L formulation.

I recognise the arguments against this such as the danger of excessive vomiting or the difficulty of treating vomiting patients with Fuller's Earth. However I consider the <u>potential</u> advantages in reducing mortality to outweigh these problems. Also from the dog studies a 50 kg patient would have to drink 500 ml 'Preglox' L containing 0.1% PP796 before they would have taken 10 mg PP796/kg (ie half the dose contraindicated in the dog studies).

The draft reports on which I have based this overview are enclosed. Please note that they are not yet finalised.

I hope you find this document of some use.

Regards,

Lewis

Lewis Smith

Encs.