DRAFT

THE EFFECT OF THE ADMINISTRATION OF PP796 ON PARAQUAT TOXICITY IN THE DOG AND AN ESTIMATION OF THE EMETIC DOSE IN MAN

The emetic PP796 was added to formulations of paraquat in the late 1970's. This decision was based on the effectiveness of PP796 in reducing the toxicity of paraquat in two species of experimental animal, namely the dog and monkey (CTL/R/391). It was shown that the approximate LD_{50} of paraquat to the dog and monkey was increased by a factor between three and five and that this reduction in toxicity could be explained by a lowering of the paraquat in the plasma of animals administered with both paraquat and emetic compared with that of animals given paraquat alone (CTL/R/391). When it came to establishing the concentration of PP796 that should be added to Gramoxone, it was decided that the minimum lethal dose of formulation should contain a dose of PP796 likely to cause emesis. This dose was set at 5mg per person based on the response of a few humans who had been given PP796 when it was under development by Pharmaceuticals Division of ICI PLC as an anti-asthmatic drug. The inclusion rate in Gramoxone became 5mg/10ml of Gramoxone (CTL/R/390).

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 would be absorbed from the gastrointestinal tract into the plasma and then accumulated into the lung. It is now clear from the data collected from CTL (and elsewhere) that paraquat is absorbed rapidly from the gastrointestinal tract into the bloodstream such that the majority of the paraquat that is absorbed will be present in the blood within a few hours of ingestion and a peak concentration in the plasma is reached within one to 3hr. Therefore, to be effective in reducing the toxicity of swallowed paraquat, not only must PP796 cause effective emesis but it must do so within a very short period of time. There is good evidence that with the present inclusion rate PP796 is an effective emetic. However, it seems very doubtful that a significant percentage of paraquat poisoned patients vomit within 10min of ingestion. It can be seen from the attached draft reports of studies carried out in dogs 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 showed that:

1) The amount of emetic given to dogs alters the time to vomiting. 0.1mg PP796/kg does not cause vomiting whereas 0.5mg/kg causes vomiting within 30min and 3mg/kg or greater cause vomiting within 10min (CTL/T/2459, CTL/T/2451 and CTL/T/2471).

2) Doses of 20mg PP796/kg appear to be supermaximal and may cause harm to the dogs (CTL/T/2459 and CTL/T/2471).

3) When a toxicologically significant dose of paraquat (20mg/kg) is given to dogs along with various doses of PP796 it was found that 0.5mg PP796/kg reduced the absorption of paraquat by approximately 10-fold and 3mg/kg or 20mg/kg by approximately 50-fold (CTL/T/2471).

These data lead to the simple conclusion that, after swallowing paraquat, rapid and effective vomiting reduces the absorption of the bipyridyl and its toxicity will be reduced.

The data in man does not indicate that PP796 causes rapid vomiting (within 10min). In some cases where vomiting has been reported very soon after swallowing and emesis has been sustained, the patients have swallowed large amounts of formulation. In these cases, large doses of PP796 have been taken which induces rapid and sustained emesis. However, large amounts of paraquat will also have been consumed (this can approach x10 or x15 the LD_{50} dose of paraquat), in which case it is very unlikely that even rapid emesis will prevent the absorption of a lethal dose of paraquat.

In the context of human poisoning cases in Japan, the following approximations have been made:

If we assume,

1) The average body weight of a Japanese to be 50kg
2) The minimum lethal dose is 10ml Gramoxone (contains 5mg PP796)

then the dose level of emetic in a minimum lethal dose of paraquat is 0.1mg PP796/kg.

This is well short of the optimum concentration range of emetic found in the dog studies which lies between 0.5mg PP796/kg and 3mg/kg.

Assuming the formulation of paraquat diluted from 20% paraquat cation to 4.5% paraquat cation and 4.5% diquat cation (Preeglox L) and that the contribution of

diquat to the toxicity of the formulation is minimal, then the minimal lethal dose of Preeglox L will be in the range of 40-50ml. By increasing the dose of emetic to 40mg in 40ml (0.1%) then the dose of emetic in one mouthful (approximately 40ml) will approach 1mg/kg (i.e. 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 which contains a lethal dose of paraquat. 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 (c.f. if 40ml of Gramoxone is swallowed and 20ml vomited, a lethal dose would remain).

The combination of the data from the dog studies together with our understanding of the absorption of paraquat in man leads to the conclusion that very rapid emesis (within 10-15min) ought to be effective in reducing the toxicity of Preeglox L. On the basis of the calculations given before it would appear sensible to add at least 0.1% PP796 to the Preeglox L formulation in order to optimise the likelihood of very rapid emesis in cases of human poisoning.

It has been suggested that an increase in the concentration of emetic in Preeglox L from that which is in Gramoxone may lead to the danger of excessive vomiting or difficulty in treating vomiting patients with Fullers Earth or other appropriate absorbants. However, the potential advantages in reducing the overall mortality rate by the introduction of 0.1% PP796 Preeglox L formulation appear to greatly outway these possible problems. Furthermore, from the dog studies, a 50kg patient would have to drink 500ml Preeglox L containing 0.1% PP796 before they would have taken 10mg PP796/kg. This is half the dose level indicated in the dog studies. In addition, it is extremely rare for patients to drink such large volumes of paraquat containing formulation.

In conclusion, an assessment of the available data on the effectiveness of PP796 in inducing vomiting together with the understanding of the pharmacokinetics of paraquat in cases of human poisoning leads to the conclusion that increasing the concentration of PP796 to 0.1% in Preeglox L is fully justified.

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