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SUMMARY OF EFFECT OF PP796 ON PARAQUAT TOXICITY

RIC4219

Death from paraquat poisoning has occurred in man as a consequence of both accidental and deliberate ingestion of paraquat formulations. The LD50 in man has been estimated to be approximately 30 mg of paraquat cation/kg body weight, equivalent to 10-15 ml of the 20% (w/v) paraquat concentrate to an adult man.

Stenching agents have been added to the formulation in the hope of reducing the risk of accidental ingestion. To increase the chances of preventing accidents or suicidal ingestion still further, it would be desirable to reduce the toxicity of the formulation. The addition of an effective emetic agent might be one way of achieving this, but such an emetic would have to be a) potent following oral administration b) of low toxicity c) stable in a mixture with paraquat and d) effective as an emetic in the presence of paraquat.

An ICI Pharmaceuticals Division compound, ICI 63197, originally developed for the relief of asthma, was shown after clinical trials in man to have a potent emetic action. This compound, reclassified as PP796 by ICI Plant Protection Division, has the necessary properties and is so potent that only small, toxicologically insignificant quantities are needed in 'Gramoxone' formulations.

This emetic, together with paraquat has been administered to male beagle dogs and cynomolgus monkeys in order to assess the effect on paraquat absorption and toxicity.

Monkeys were dosed with 100 mg paraquat ion/kg in 20 ml solution. This solution contained 10 g 'Complan' (a skimmed-milk powder) in an attempt to reduce irritancy to the stomach. PP796 was added, as appropriate, to give 2 mg/kg body weight. Dogs were dosed with 20 or 30 mg paraquat ion/kg and either 2 or 3 mg PP796/kg.

Animals were dosed by stomach tube with paraquat either with emetic or without; they were then observed and the time taken to vomit recorded. Blood samples were taken at intervals for paraquat measurement.

Eight monkeys dosed with 100 mg of paraquat cation/kg body weight but without PP796, died within the first few days of dosing, despite vomiting between 3 and 5 hours of being dosed. 6 of the 8 monkeys dosed with the same amount of paraquat containing PP796 vomited within an hour and these animals survived.

The concentration of paraquat in the plasma of monkeys dosed with paraquat plus emetic was considerably less than that in the plasma of monkeys dosed with paraquat alone.

None of the dogs dosed with either 20 or 30 mg of paraquat cation/kg body weight vomited and 3 out of each group of 4 died between 4 and 8 days after dosing. All 8 dogs dosed with these levels of paraquat containing PP796 vomited within one hour of dosing and survived.

The concentration of paraquat in the plasma of dogs dosed with paraquat plus emetic was considerably less than that in the plasma of dogs dosed with paraquat alone.

In a further experiment, the LD50 to monkeys of paraquat formulated with 10% wetting agent, 1% pyridine stench and an emetic dose of PP796 was in the range of 250-500 mg/kg body weight.

This work shows that 2-3 mg of PP796/kg body weight is clearly an emetic dose to monkeys and dogs, usually causing vomiting within an hour of dosing. This action does not appear to be affected by the presence of a 15-50 fold excess of paraquat. As a consequence of vomiting, the absorption of paraquat is considerably reduced and animals survive an otherwise lethal dose of paraquat.

The administration to monkeys of paraquat formulation (containing no added emetic) also resulted in vomiting after a delay of many hours but this did not lead to the survival of the animals. Thus, for emesis to be effective, it must occur within an hour of administration of the paraquat.

The LD50 of paraquat without emetic to monkeys has been shown to be approximately 60-70 mg/kg body weight. The presence of an emetic dose of PP796 raises this value to 250-500 mg/kg body weight, thus reducing the toxicity of paraquat by a factor of approximately 5.

In conclusion; therefore, it is clear that the inclusion of an emetic dose of PP796 to a formulation of paraquat reduces the absorption of paraquat and thus significantly reduces the toxicity of the formulation.

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 swallowing 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 '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.

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'GRAMOXONE' : THE EMETIC FORMULATION

1. INTRODUCTION

Since its introduction in 1962 to the herbicide market 'Gramoxone' has become one of the most widely used herbicides in world agriculture. When used as recommended it has also established a firm record of safety. The sale of 'Gramoxone', with the support of Plant Protection Division, is legally restricted in most countries to bona fide distributors and farmers. This restriction has not totally prevented the unauthorised possession of the product by members of the public who often wish to take advantage of the excellent herbicidal properties of 'Gramoxone'. Regrettably such unauthorised possession frequently results in the product being transferred to various alternative containers such as drinks containers.

This malpractice has lead, in a number of cases, to accidental deaths when innocent persons have consumed the contents of a bottle believing it to contain innocous material. The adverse publicity given to deaths from 'Gramoxone' has probably been a contributory factor in causing its deliberate use as an agent of suicide.

Although deaths from paraquat poisoning are not numberous and occur in relatively few countries in the world, the recognition by ICI Plant Protection Division that the mis-use of 'Gramoxone' had, on occasion, caused it to be accidentally swallowed, with ensuing fatal consequences, has lead ICI to search for measures to reduce this hazard.

An ICI team, comprising experts of Plant Protection Division and Central Toxicology Laboratory, was therefore charged with the specific objective of altering the formulation of 'Gramoxone' so that swallowing it would have less toxic consequences. This team identified that an <u>effective emetic agent</u> could have substantial advantages in meeting this objective. An emetic would be a safety measure which could cover all situations, children and adults, accidents or suicides. However, to be of value for 'Gramoxone' the emetic would have to satisfy a number of important criteria.

2. SELECTION CRITERIA FOR AN EMETIC AGENT AND ASSESSMENT OF KNOWN EMETIC AGENTS

The principal criteria deemed necessary for an emetic agent to be of practical value for addition to paraquat formulations were as follows:

1. Speed and Mode of Action

The emetic agent must produce a rapid vomiting response prior to the absorption of toxic amounts of paraquat. It should act centrally and not produce its action by irritant effect upon the gastric system. Irritancy could potentiate the absorption of paraquat.

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2. Specificity

The agent should demonstrably be able to act in the presence of paraquat ie appropriate animal experiments must provide evidence that paraquat does not interfere with the emetic action.

3. Safety

The agent should be toxicologically acceptable and harmless to the user.

4. Environment

The agent should be without harmful effect upon the environment.

5. Stability

The agent should be stable in the presence of paraquat and <u>vice</u> versa. In addition it should not interfere with the herbicidal properties of paraquat.

With these criteria in mind an assessment was made of emetic agents contained in literature reference (eg references 1,2) and those currently used in European and American medical practice.

These agents fall into two distinct classes, those emetics which, through inherent toxicity and unreliability are no longer used, and two remaining agents, apomorphine and ipecacuanha which are still widely employed for the treatment of poisoning.

The agents which are now excluded from modern medical practice are as follows:

1. Matricaria

This is the ground flower heads of the chamomile plant. It is irritant in action, unreliable and, being insoluble in water, would be of no practical value for paraguat formulations.

2. Mustard

This agent, which is also highly irritant is insoluble in paraquat.

3. Oil of Mustard

This agent, the active principle of mustard, has not been used as an emetic agent. A proposal to use it in France for formulations of paraquat originating from Taiwan was withdrawn. Oil of mustard is a severe skin irritant and experience with such compounds suggests that they can increase dermal adsorption. This could introduce a risk of uptake of paraquat through the skin if contamination took place during spraying operations. 4. Salts of Heavy Metals eg Copper, Antimony and Zinc

These agents are firmly outlawed by modern medical opinion because of their high toxic risk (reference 2). In addition they would not be environmentally acceptable.

5. Sodium Chloride

This agent, commonly used in domestic poisoning incidents is no longer generally recommended. Its efficacy is variable and a number of deaths have occurred following its use.

6. Squill

This agent, used on rare occasions in the past, is highly irritant in action and can produce cardiac irregularities.

The emetics still employed in medical practice are:-

1. Apomorphine

This agent, although highly effective, can only be administered by intramuscular injection. It is unstable in air. For these reasons it is of no practical value for paraquat formulations.

2. Ipecacuanha

This agent is widely used as an orally adminstered emetic. It acts on the central nervous system but is also a gastric irritant. In excessive amounts (approximately 10 x the emetic dose) fatalities have occurred.

Despite its lack of general recommendation (reference 1) ipecacuanha was given serious consideration for addition to paraquat formulations. A study in monkeys was undertaken at the Huntingdon Research Centre, England to evaluate the potential of this agent. It was found (reference 3) that ipecacuanha was unpredictable in response and was only effective at doses associated with toxic symptoms. It was a conclusion of the authors of the Huntingdon study that "This compound would not be of value if added to a toxic material in an attempt to reduce toxicity by vomition". On the basis of these findings it was decided to reject ipecacuanha as agent for paraquat.

3. DISCOVERY AND DEVELOPMENT OF A NEW EFFECTIVE EMETIC AGENT (PP796)

It was clear therefore that no known emetic substance could be added to paraquat which would be predictably safe and effective.

Fortuitously, the team was informed of a compound under development by ICI Pharmaceuticals Divison for the control of asthma which had been discovered, in the course of human trials, to be a potent emetic agent. Development as a drug was terminated and the compound now coded PP796, was exhaustively examined for a new role as an emetic in conjunction with paraquat.

In summary the outcome of considerable research with PP796 has shown it to be a compound of low mammalian toxicity and high emetic potency, even in the presence of paraquat.

Monkeys have been shown to survive three times a normally lethal dose of paraquat when administered in the presence of PP796. Emesis is rapid, vomiting usually occurring within 15 minutes by an action which is understood to be centrally mediated.

PP796 has the additional property, at sub-emetic doses, of reducing the rate of gastric uptake for a period of four hours following dosing. This property, in conjunction with emesis, should play an important role in the critical period following the ingestion of paraquat.

PP796 is without environmental effects at the low concentration present in diluted 'Gramoxone' (5 ppm) and has no effect upon the herbicidal action of 'Gramoxone'. It is stable in 'Gramoxone' under all normal conditions of storage. Extensive user experience of the new formulation has confirmed the predicted absence of any additional hazard posed by the incorporation of the emetic agent.

4. CONCLUSIONS

The properties of PP796 with respect to use with paraquat are unique compared to other known emetic agents and, unlike other emetic agents, PP796 has met all the technical criteria judged necessary for addition to paraquat formulations. In addition, it has been shown to have a delaying effect on gastric emptying, a property which additionally limits the toxicity of paraquat and provides support for the more effective treatment of human poisoning cases.

(1) Insert the following sentence, where applicable:

A separate dossier containing the relevant experimental data on PP796 as an effective emetic agent in paraquat formulations has been (will be) submitted for consideration by the appropriate authorities.

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On the basis of its safety and the substanial body of animal data indicating that its use should be of benefit to humans, ICI has adopted the policy of registering formulations of 'Gramoxone' containing PP796 as widely as possible. The potential benefits of the new, emetic, formulation have been recognised

- ** by some authorities as a major step resulting in their making mandatory the addition of an effective emetic agent to paraquat formulations.
 - ** This last sentence should not be included in submissions to countries where this is judged to be detrimental to our case, ie to fend off competitive paraquat not containing an effective emetic.

5. REFERENCES

- 1. Matthew H and Lawson A A H, 2nd Edition 1972 'Treatment of Common Acute Poisonings'. London. Churchill Livingstone.
- 2. 'Drug Evaluations' 3rd Edition 1977, American Medical Association, Baltimore.
- Grimshaw P, Purser D A and Cob L M, (1979), 'The emetic activity of liquid extract of ipecacuanha BP in cynomolgus monkeys'. Huntingdon Research Centre Report ICI 150/79446.

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