COMPANY SECRET HIGHLY CONFIDENTIAL

REPORT OF WORKING PARTY ON THE FEASIBILITY OF ADDING AN EMETIC TO GRAMOXONE

Thursday, 29 January 1976

Composition of Working Party:

Dr G E Davies, Biology Dept, Pharms. Div.
Dr G M R Samuels, Central Nervous System Group, Pharms. Div.
Dr J T Nicholls, Clinical Research Dept, Pharms. Div.
Dr D M Foulkes, Plant Protection Division
Dr M S Rose, Central Toxicology Laboratory

Apologies were received from Dr Foulkes who was unable to attend.

Aims: To examine the feasibility of adding an emetic to Gramoxone and to suggest a programme of work which would provide the necessary information on which to take a decision on the viability of the idea.

Conclusions:

1. It was accepted that induction of vomiting shortly after ingestion of lethal doses of Gramoxone should reduce the amount of paraquat available for absorption and thus lower the toxicity of the formulation.

2. A number of existing emetics were considered: ipecacuanha, apomorphine, copper sulphate and the pharmaceutical compound 63197.

Ipecacuanha

This emetic is already formulated with some barbiturates (trade name Phenemetic). However, its efficacy is said to be variable and there is the suggestion that vomiting can be uncontrolled (Martindale). It is an irritant and thus might be an undesirable additive to a formulation containing paraquat. The active ingredient is emetine. Deaths have occurred as a result of overdosing (Martindale).

Apomorphine

A very effective, centrally acting emetic which is usually given by subcutaneous injection. Overdosing with apomorphine can lead to profound CNS effects which can culminate in death (Martindale). Excessive vomiting can be stopped by intramuscular injection of chlorpromazine or phenothiazine.

Copper Sulphate

Copper sulphate is an irritant emetic which is also rather toxic. Large doses (250 mg) are required for its action, which can be delayed.

63197

63197 is a phosphodiesterase inhibitor developed by Pharmaceuticals Division as a bronchodilator. It is a potent, centrally acting emetic, causing

vomiting in man with oral doses of the order of 5 mg. It is of relatively low toxicity. Although it is not a generally recognized emetic agent, there is considerable pharmacological and toxicological information on the compound. It has been shown not to be carcinogenic. It has been submitted twice to the Committee on Safety of Medicines and has received approval for clinical trials.

3. It was decided that an emetic should, if possible, be chosen from amongst the group of compounds discussed. A synthetic programme to discover a novel compound would be very time-consuming and even if successful would require considerable effort to generate the necessary toxicological and pharmacological information to enable it to be used.

The compounds were examined for their suitability against the following criteria:

(a) low toxicity - since it would not be possible to limit the dose that an individual might take, it is clearly important that the compound is not too toxic although it was recognized that a lethal dose of paraquat was being consumed at the same time!

(b) fast-acting.

(c) non-irritant - an irritant emetic would probably give rise to GI tract problems in the presence of Gramoxone which is already an irritant. Moreover, the absorption of residual paraquat might be enhanced.

4. 63197 was chosen as meeting all of the above criteria. If an emetic dose is estimated at 5 mg then it was felt that a suitable concentration in the formulation would be 5 mg in 25 ml or 20 mg/100 ml Gramoxone. Thus an attempted suicide with 100 ml of Gramoxone or more should vomit copiously.

Proposed Programme of Work

Phase 1	ACTION
1) Check availability and approximate cost of 63197.	MSR
2) Check compatibility with paraquat and the Gramoxone formulation - stability - solubility (at 20 mg/100 ml)	JHRS PPD
3) Check emetic effect of 63197 in paraquat poisoned dogs and whether toxicity is lowered.	CTL
Phase 2	
4) Study whether excessive vomiting can be stopped with agents such as promethazine, chlorpromazine, metachlopramide.	CTL
5) Study effect of 63197 on paraquat toxicity in rats.	CTL
6) Study effect of paraquat on absorption, plasma levels etc of 63197 (in rats).	CTL
7) Check effect of 63197 on paraquat absorption, plasma levels, lung uptake etc (in rats).	CTL

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ACTION

8) Study effect of 63197 on plasma paraquat in dogs. CTL

9) Environmental effects of 63197/residues etc. JHRS PPD

Availability and Cost of 63197

There are 100 - 200 g of 63197 currently available. Synthesis is not difficult but involves the use of hydrazine which is classified as a carcinogen. Dr Purchase has pointed out that this does not mean that it would not be possible to manufacture 63197 but that the process would have to be carefully examined for hazard and the final product would have to be examined for contamination and possible breakdown.

The cost of manufacture has been roughly estimated to be £30 - £50/kg.

Summary

The Working Party considers that an emetic added to Gramoxone would make the formulation safer.

63197 has the requisite properties for such an emetic. A programme of work required to assess 63197 has been proposed

A decision has to be made by PPD whether this programme should be undertaken.

Circulation: Those present at the meeting
Dr A A B Swan

MSR:SDL
9 Feb 76

P/2/116

2/6/76

Plasma samples for latest experiment 100 mg/kg paraquat + 2 mg/kg emetic

Same dosing solution as for previous 4 animals

301 and 299 vomited within 30 minutes
297 after 50 minutes
303 1 fl. after 2 hrs 10 mins

Dear Mike,

Unfortunately one animal was rather late in responding to the emetic, perhaps we should increase the emetic dose further. I will let you know how the situation develops later in the week.

Dave Purser.

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