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'GRAMOXONE' POISONING IN THE UK 1980-1988

AND THE ROLE OF THE EMETIC

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SUMMARY

1. The emetic causes a more reliable and increased incidence of vomiting within half an hour of ingestion.

2. A beneficial effect of the emetic in reducing 'Gramoxone' ingestion fatalities has not been demonstrated. This seems likely to be because the vast majority of poisoning cases in the UK now relate to deliberate ingestion with suicidal intent, when relatively large (>25 ml) volumes are swallowed.

3. The addition of emetic to paraquat may have some value in preventing serious poisoning when relatively small quantities (<25 ml 'Gramoxone') are swallowed, i.e. in the case of accidents. The presence of emetic does not increase the toxicity of paraquat and consequently there is no justification for abandoning this approach to prevention.

INTRODUCTION

Paraquat has been used widely in the world for some 30 years. It is sold mainly as 'Gramoxone', a 20% w/v aqueous formulation. While there is no significant health problem during normal occupational exposure, human poisonings have occurred through ingestion, mainly of undiluted concentrate. No cases have been reported of death following the ingestion of spray-strength material.

Several measures, such as the introduction of alerting agents - (colour and smell) into the liquid formulation have helped to reduce accidents, so that the overwhelming majority of poisoning incidents now arise through deliberate swallowing of the product, i.e. with suicidal intent.

An emetic agent, invented by ICI and coded PP796, was introduced in 1978 to prevent a lethal dose of paraquat being absorbed once it was swallowed - a built-in first aid measure. Ingestion of 'Gramoxone' itself causes emesis in many cases but the presence of emetic was intended to increase the incidence of vomiting and also reduce the time taken for vomiting to occur. These benefits were clearly demonstrated in animals (dog and monkey); inclusion of emetic into 'Gramoxone' resulted in a 3-5 fold reduction of its toxicity to these species. The emetic causes the amount of paraquat in the stomach to be reduced and consequently less to be absorbed into blood. An analysis of the concentration to paraquat in plasma from human poisoning cases showed that there was a relationship between the concentration of paraquat present in plasma and mortality. Those patients with paraquat plasma levels below 0.3 ug/ml, 24 hours after ingestion have a greater chance of survival.

SELECTION OF EMETIC

The specific emetic used was developed by ICI because none of the traditional emetics could fulfil the stringent requirements of a material to be incorporated into 'Gramoxone'. Syrup of ipecacuanha is widely used as an ematic. However, it was found to be unpredictable in response and slow acting. Furthermore it can hasten the passage of certain materials into the small intestine, from where paraquat is mainly absorbed. Sodium tripolyphosphate (STP) is also widely used as an emetic. It was much slower acting than PP796, even when used at 30 times the concentration of the latter. Moreover, STP acts as a stomach irritant which could stimulate absorption of paraquat. This is in contrast to PP796, which is absorbed and acts centrally. 'Gramoxone' itself is an irritant to the stomach and often causes emesis on its own. However, the vomiting response is variable and the addition of PP796 was intended to provide a more consistent and rapid emesis.

Man was shown to be more sensitive in response to the emetic than dogs or monkeys, and a dose of 5 mg was judged to be adequate to induce emesis reliably. A volume of 10 ml 'Gramoxone' is considered to be the smallest volume containing a possible lethal amount (2g) of paraquat to man. Therefore the emetic was included in 'Gramoxone' at a concentration of 0.05% w/v, so that a person ingesting the minimal lethal volume (10 ml) would also receive an effective dose (5 mg) of emetic. Clearly people ingesting larger volumes of 'Gramoxone' would automatically receive larger doses of emetic.

The mode of action, toxicology and lack of effect on herbicidal activity of PP796 have been investigated extensively. On these grounds 'Gramoxone' containing emetic has been accepted for use in all the major countries of Europe and North America.

A preliminary report from the UK National Poisons Information Service (NPIS) from UK data (1980-88) suggested that the presence of emetic may be associated with some reduction of mortality (Denduyts-Whitehead et al, 1985). The evidence accumulated more recently for the same period is now reviewed.

METHODS

The methods of data collection by the UK National Poisons Information Service (NPIS) and the development of a computerised data base on human cases of paraquat poisoning in the UK are described in the paper by Northall et al (1992).

Cases were selected for the data base only if:

(i) the identity of the product was known and the presence or absence of emetic was known (from analysis or label)

(ii) Exposure to paraquat was by the oral route

(iii) the final outcome of the case was known.

Cases were categorised according to whether 'Gramoxone' or the low strength granular home and garden product was involved. This review of the results presents only the data derived from poisonings involving 'Gramoxone' or other concentrated liquid formulations containing paraquat. The results include data up to 1988 only, since from that date no non-emeticised products were recorded as being involved and the "not knowns" represented 81-97% of all reported cases for the later period 1989-91.

RESULTS AND DISCUSSION

From information collected by NPIS on circumstances of poisoning with pesticides it is apparent that many people store partly-used containers of pesticides, maybe for years. The time taken for the old paraquat formulation to be completely replaced by the new one thus inevitably shows a lag phase. This is reflected in the numbers of poisonings using the old (non-emeticised product) which occurred in the period 1980-1988, several years after introduction of the emeticised product into the market. Eg.

Number of Cases of Ingestion in the Period 1980-88, Involving Commercial Paraquat Products

With Emetic	Without Emetic	Total
51	42	93

Incidence and Mortality

There were 93 cases of poisoning from liquid paraquat concentrate in the 9 years of the study, where paraquat ingestion was proven and outcome known (see above and table 1). Of the 51 persons known to have swallowed the emetised product, 37 died, a mortality rate of 72.5%. Howard (1977) summarised paraquat incidents and outcome for the period before emetic had been introduced and reported 36 deaths from 41 cases, a mortality incidence of almost 88%. It is difficult to compare this result with the mortality incidence (72.5%) resulting from emeticised product, especially in view of the lower mortality incidence (64%) of those taking the non-emeticised during the same period (Table 1).

The results of the 1980-88 survey thus seem to suggest that the emetic is having no effect in reducing the percentage fatalities in people who ingest 'Gramoxone'. This is almost certainly because of the relatively small numbers of people who ingested less than 25 ml product (Table 1). It is accepted that the emetic is not likely to be helpful in the majority of cases where larger quantities of paraquat are swallowed, since the proportion left in the digestive tract after emesis, although a small amount in relation to that originally ingested, is still likely to represent a lethal quantity.

Furthermore, the volume of product reported to have been swallowed is subjective and open to significant error. Generally the tendency is to underestimate the actual volume swallowed. (A mouthful of liquid can range from 20-30 ml). Hence it is likely that the numbers of cases categorised as taking <25 ml are in fact even smaller than those listed in Table 1.

There is a further uncertainly in the data, which relates to the number of cases for which the outcome was not resolved. This was 34% of all cases for all paraquat products but is closer to 10% for the commercial liquid products. It seems more likely that the outcome would not be notified if the patient recovered than if he died, and that the percentage mortality would consequently be expected to be lower than the figures in Table 1 show. In fact it is accepted by NPIS that "outcome not known" indicates survivors. Fatal outcomes are always notified.

Nevertheless it must be accepted that the only conclusion which can be drawn from the actual data, is that a beneficial effect of the emetic in reducing 'Gramoxone' ingestion fatalities has not been demonstrated. Despite this, the emetic retains a potential to be of benefit in the marginal cases, where small volumes are ingested, notably of accidents. The benefits also include early warning of a serious problem, viz by causing vomiting.

Speed of Emesis

Further details of the outcome after ingestion of 'Gramoxone' related to the incidence of vomiting are shown in Table 2. The figures in the first column refer to the numbers of patients reported to have vomited within 30 minutes of ingesting the product. Here there is a clear indication that the presence of emetic increased the speed of emesis, eg.

	Total cases for which time to vomiting was noted	Vomited within 30 min	%
With Emetic	21	11	52
Without Emetic	16	5	31

Speed of emesis is important in removing paraquat from the stomach quickly and so helping to avoid high paraquat levels in plasma developing. Nevertheless the increase in speed of emesis is not reflected in a significant decrease in total mortality. (69% for those vomiting within ½hr compared with 76% for those known to vomit later than ½hr after ingestion), Table 2.

Again there are too few individuals ingesting non-emetic product and vomiting within ½hr to give a reliable mortality rate so the influence of emetic on mortality rate for patients vomiting within ½hr is impossible to assess.

Unfortunately, the data does not show the volumes of 'Gramoxone' ingested by the groups who vomited in less than ½ hr or after ½ hr. The majority of the cases vomiting in less than ½ may well come from the group ingesting more than 25 ml since these comprise at least 75% of the total cases (Table 1). For this reason one would not expect to see a significant difference in mortality rate between the "no emetic" and "with emetic" group, as discussed above.

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A limited amount of data relating volume swallowed, with or without emetic to speed of emesis is available from the NPIS for the period June 1980-Nov 1981. This is shown in Table 3. The numbers of cases (9) for those ingesting emeticised product is again quite small, partly due to the limited period (12 months) and also the lag in clearing non-emeticised product from market circulation. Nevertheless, the 9 persons swallowing emeticised product all vomited; 8 of them within ½hr of ingestion. Of the 17 persons ingesting non-emeticised product only 4 vomited within ½ hr and 13 were recorded as not vomiting at all. Because of the way the data is presented it is not possible to relate these early and late vomiting cases to survivors or fatalities.

REFERENCES

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Table 1.

Reported Dose of 'Gramoxone' Swallowed and Outcome (1980-1988)

Volume of Product Swallowed*					
Product	<25 ml	>25 ml	Not known	Total	% Mortality
No Emetic					
deaths	5	20	2	27	
cases	13	25	4	42	64
With Emetic					
deaths	4	29	4	37	
cases	8	37	6	51	72.5
Totals					
deaths	9	49	6	64	
cases	21	62	10	93	69

* 25 ml contains 5g paraquat
2-3 gm paraquat is about LD_{50}

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Table 2.

Time to Vomiting and Outcome After Ingestion of 'Gramoxone' Products With or Without Emetic (1980-88)

Product	<½ hr	>½ hr	Time not known	Did Not Vomit	Not known if vomited	Total
No Emetic						
deaths	3	9	7	-	8	27
cases	5	11	11	-	15	42
With Emetic						
deaths	8	7	10	-	12	37
cases	11	10	10	-	20	51
% Mortality with or without emetic	69	76	-	-	-	69

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Table 3.

Spontaneous Vomiting After Ingestion of Emeticised/Non-emeticised 'Gramoxone' Products (1980-1981)

Volume Ingested	Early Vomiting <½ hr	Late Vomiting	No Vomiting	Cases
No Emetic				
<25 ml	1	1	6	8
25 - 50 ml	1	1	4	6
>50 ml	2	-	3	5
With Emetic				
<25 ml	1	1	0	2
25 - 50 ml	1	0	0	1
>50 ml	6	0	0	6

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Table 4.

Number of Cases Per Year of Deliberate Ingestion of Paraquat (all products) by Adult (>12 years), Showing the Outcome

Year	Died	Survived	Outcome not known	Total	% Fatality *
1980	33	46	6	85	39
1981	37	40	-	77	48
1982	31	55	2	88	35
1983	31	61	5	97	32
1984	32	47	5	84	38
1985	18	22	8	48	38
1986	17	29	13	59	29
1987	16	20	15	51	31
1988	11	29	18	58	19
1989	7	23	5	35	20
1990	6	24	22	52	12
1991	9	18	15	42	21
Totals	247	403	114	764	

* Assuming those "outcome unknown" survived.

Table 5.

Number of Cases per Year of Accidental Ingestion of Paraquat (all products) by Adult (>12 years), Showing the Outcome

Year	Died	Survived	Outcome not known	Total	% Fatality *
1980	3	4	2	9	33.3
1981	2	4	2	8	25
1982	1	12	2	15	6.6
1983	0	3	4	7	0
1984	0	8	1	9	0
1985	0	3	-	3	0
1986	0	4	2	6	0
1987	2	5	2	9	22
1988	0	5	2	7	0
1989	0	-	1	1	0
1990	0	-	2	2	0
1991	0	2	2	4	0
Totals	8	50	22	80	

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