NAKAMURA 855

77

H-7. EFFICACY OF GUT LAVAGE IN THE REMOVAL OF PARAQUAT IN THE DOG

K Nakamura, MD; M Yamashita, MD; and H Naito, MD
Institute of Clinical Medicine, University of Tsukuba, Sakura-mura, Niihari-gun, Ibaraki-ken 305, Japan.

A potent emetic has been recently added to the paraquat formulation to reduce the paraquat toxicity by producing strong vomiting after ingestion. Nevertheless, there is no clear evidence that the emetic has reduced the mortality from paraquat since the emetic was added to the paraquat formulation. In our poison control center, the mortality was 90% in the last 11 months. Our collected data show that most patients ingested large doses of paraquat for suicide attempts, which is much more than the smallest fatal dose in man. A question which came up is that enough paraquat for producing toxicity might be still in the gastrointestinal tract even after vomiting when a large dose of paraquat was ingested. It was the purpose of this experiment to estimate how much paraquat would be removed from the intestine using gut lavage in the dog dosed with paraquat either with the emetic or without the emetic.

MATERIALS AND METHODS

Eleven mongrel dogs weighing 10-23 kg were starved for 24 hours before the dogs were anesthetized with 10-15 mg of ketamine hydrochloride/kg body weight intramuscularly. Animals were dosed through a gastric tube with paraquat dichloride either with the emetic or without the emetic after the stomach content was aspirated. The gastric tube was removed immediately after the administration of paraquat. The dogs were kept in a frame. The paraquat dosing solution consisted of the appropriate volume of paraquat diluted with water into a total volume of 50 ml so that animals received 250 mg of paraquat dichloride/kg body weight. The paraquat used in this experiment was a commercial preparation containing 24% paraquat dichloride and 0.05% emetic, PP796, in water. Paraquat with the emetic was given to 5 dogs and paraquat without the emetic to 6 dogs.

The upper duodenum and rectum were ligated 4 hours after paraquat administration under general anesthesia with ketamine, then the gut was lavaged for 20 min using 2,000 ml of warm water through duodenostomy. Lavage fluid was collected through sigmoidostomy to calculate the amount of paraquat in the fluid. Per cent recovery of paraquat from lavaged fluid was expressed by percentage of the amount of paraquat administered.

Table 1. Plasma Concentration of Paraquat (μg/ml)

Group	1 hr*	2 hr*	4 hr*
Paraquat+Emetic (n = 5)	124.5±43.9	72.9±40.8	23.7± 6.7
	NS	NS	NS
Paraquat (n = 6)	122.7±73.1	82.3±41.6	52.9±36.2

*Mean±SD NS: Not Significant

Per cent recovery of lavage fluid was also expressed by percentage of 2,000 ml of warm water given through duodenostomy.

Venous blood samples for the measurement of paraquat in plasma were taken 1, 2, and 4 hours after administration. Paraquat in both plasma and lavage fluid were analysed using radioimmunoassay. The difference of mean values between the two groups was tested using Student's t-test.

RESULTS

All dogs vomited within the first 15 min of dosing in the "paraquat with emetic" group, on the other hand, around 1 hour after administration in the "paraquat without emetic" group. Paraquat concentrations in plasma 1 hour after dosing marked the highest levels, then gradually declined (Table 1). Paraquat concentrations in plasma at each sampling point were not significantly different between two groups.

Table 2 shows per cent recoveries of lavage fluid and paraquat from the lavage fluid in both the "paraquat with emetic" group and the "paraquat without emetic" group. Per cent recoveries of both lavage fluid and paraquat from lavage fluid were not significantly different between the two groups.

DISCUSSION

By using our method, we presume that the estimation of the amount of paraquat which is present in the intestine 4 hours after administration is fairly reliable, firstly, because the gut lavage was performed from the upper duodenum through the lower sigmoid. Secondly, as the time consumed for the gut lavage was 20 min, it is unlikely that a significant amount of paraquat was lost from the intestine by absorption during the period of gut lavage. Thirdly, since recoveries of lavage fluid in both groups were 94.5 ± 3.7% and 101.7 ± 12.9%, it is unlikely that a significant amount of the lavage fluid was retained anywhere in the intestine. The procedures of gut lavage in both groups seems identical.

The results of our experiment indicate that the amount of paraquat which was present in the intestine 4 hours after oral administration was only 3-4% of the dose given.

Table 2. Per Cent Recovery of Paraquat and Lavage Fluid

Group	Lavage Fluid*	Paraquat*
Paraquat + Emetic (n = 5)	94.5± 3.7	2.5±1.0
	NS	NS
Paraquat (n = 6)	101.7±12.9	4.3±4.5

*Mean±SD NS: Not Significant

Two possibilities seem to explain this finding. First, as most of the paraquat administered might have been absorbed from the intestine soon after administration, the amount which was left in the intestine 4 hours after administration is only fragmental. The highest plasma levels of paraquat were noted 1 hour after administration in our experiment, which might explain this assumption. Second, as a large percentage of paraquat might be still in the stomach even 4 hours after administration, the amount of paraquat which entered into the intestine was only fragmental. Smith and coworkers have shown that between 10% and 40% of orally administered 680 µmol/kg of paraquat was found in the stomach of rats even after 16 hours. Besides, a large dose of paraquat such as the 250 mg/kg used in our experiment is likely to depress gastrointestinal motility and thereby cause delayed entry of paraquat into the intestine.

The results of our experiment also indicate that there is no significant difference between the two groups in per cent recoveries of paraquat which are quite small, 2.5% and 4.3%. Therefore it is questionable that any effects of vomiting could produce any significant effects on these small fractions of administered dose. The efficacy of gut lavage 4 hours after oral ingestion of a large dose of paraquat seems quite questionable since the removal is up to 4% of the total dose given.

In conclusion, when 250 mg/kg of paraquat was given, the emetic did not reduce the amount of paraquat in the intestine compared to the amount after paraquat without the emetic. Plasma concentrations were the same in both groups. Between 3% and 4% of paraquat administered into the stomach was removed using gut lavage 4 hours after administration.

H-8. REDUCTION OF PARAQUAT TOXICITY BY N-ACETYL-L-CYSTEINE

Shu Shum, MD, Thomas W Hale, PhD, and Rolf Habersang, MD
Department of Pediatrics, Texas Tech University Health Sciences Center
Amarillo, Texas 79106

The in vivo biotransformation of relatively inert compounds to highly cytotoxic intermediates is now recognized as the initial event in the cytotoxicity of a number of common products including paraquat. Highly reactive intermediates may then react with cellular components in a number of ways including peroxidation of lipid membranes. Bus et al (1) recently demonstrated evidence of lipid peroxidation by paraquat in pulmonary tissue.

Paraquat undergoes a single electron reduction to form the reduced radical with microsomal NADPH serving as the source of electrons (2). Reduced paraquat is then reoxidized and the superoxide radical formed. The superoxide radical then dismutates to singlet oxygen which then may peroxidize polyunsaturated membranes to produce lipid hydroperoxides. The spontaneous decomposition of lipid hydroperoxides initiates the chain reaction process of lipid peroxidation. Figure 1 illustrates the mechanism whereby endogenous antioxidants may interrupt the lipid peroxidative chain reactions introduced by paraquat. Superoxide radicals are first converted by superoxide dismutase to ground state molecular oxygen and hydrogen peroxide (3). Hydrogen peroxide is then further detoxified by catalase. Antioxidants such as vitamin E presumably terminate the lipid peroxidative chain reaction (4). Finally, glutathione peroxidase reduces unstable lipid hydroperoxides to lipid alcohols by oxidizing reduced glutathione thus preventing the formation of lipid free radicals that lead to membrane damage (5).

The clinical use of superoxide dismutase in acute paraquat poisoning has been disappointing in spite of the experimental evidence indicating a protective effect (6). Because superoxide dismutase is a large protein, it does not readily penetrate cell membranes. Further it is rapidly inactivated in vivo. These factors probably explain its lack of therapeutic efficacy. Vitamin E also suppresses superoxide radicals as well

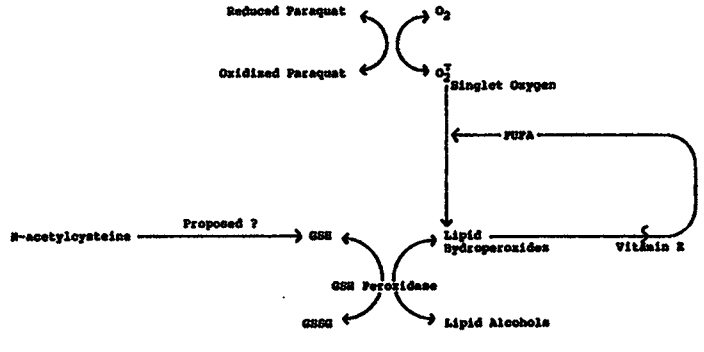

Fig 1 - Adapted from Bus et al (1975).