Pyrazole as an Antidote for Ethylene Glycol Poisoning.

MUNDY, R. L., HALL, L. M. and TEAGUE, R. S. (1974). Toxicol. Appl. Pharmacol. 28, 320-322. Pyrazole, a potent alcohol dehydrogenase inhibitor, given ip to mice in a single dose of 300 mg/kg increased the LD50 of orally administered ethylene glycol from 12 ml/kg to 22 ml/kg. This finding lends significant indirect support to the idea that a portion of the toxicity of ethylene glycol is due to metabolism of the parent compound to more toxic products via alcohol dehydrogenase.

There is ample evidence in several animal species to show that ethylene glycol is metabolized to glycolaldehyde, glycolic and glyoxylic acids and that a minor amount of the parent compound is further degraded to oxalic acid (Gessner et al., 1961). Bove (1966) has provided anatomical evidence that each of the metabolic intermediates (glycolaldehyde, glycolic and glyoxylic acids) is capable of producing tubular oxalosis in rats. Richardson (1973) has recently emphasized the importance of the liver in the toxicity of ethylene glycol and its metabolic products in the rat.

Current therapy for ethylene glycol intoxication includes the use of ethanol as a competitive substrate inhibitor of alcohol dehydrogenase. Such therapy is effective in man and prevents conversion of the glycol to more toxic metabolites (Wacker et al., 1965).

Pyrazole is a potent alcohol dehydrogenase inhibitor which has been used experimentally to treat methanol poisoning successfully in the rat and primate (Watkins et al., 1970). It was the purpose of this preliminary work to explore the possibility of reducing the toxicity of ethylene glycol by depressing the activity of alcohol dehydrogenase by pyrazole.

METHODS

Adult, female, Swiss, albino mice obtained from Southern Animal Farms, Prattville, Alabama, weighing from 22-32 g, were used in these experiments. They were housed in plastic cages on hardwood chips and had access to food and water at all times.

Ethylene glycol (Fisher Scientific Co., CP Grade) was administered po to the mice via a 20-gauge hypodermic needle which was covered by polyethylene tubing. The covered needle, attached to a syringe, was advanced into the stomach. The mice were weighed just prior to drug administration, and the dose was calculated as milliliters of ethylene glycol per kilogram.

Pyrazole (Aldrich Chemical Co.) was dissolved in distilled water in a concentration so that 0.01 ml/g would deliver a dose of 300 mg/kg. It was injected ip immediately after glycol was administered. Unprotected mice were given 0.01 ml/kg of 0.9% sodium chloride solution ip.
The animals were observed for 5 days after the injection of the ethylene glycol. The LD50 and 95% confidence limits were determined according to the method of Weil (1952).

RESULTS AND DISCUSSION

The control LD50 value for ethylene glycol toxicity in mice obtained in these experiments were within the limits of LD50 values for the compound reported in the literature (Laug et al., 1939; Latven and Molitor, 1939).

Table 1 shows that the LD50 value in the treated group was increased to a significant degree by the therapy.

<table>
<thead>
<tr>
<th>Ethylene Glycol (ml/kg, po)</th>
<th>No pyrazole (died/tested)</th>
<th>Pyrazole* (died/tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0</td>
<td>2/6</td>
<td>—</td>
</tr>
<tr>
<td>12.0</td>
<td>3/6</td>
<td>—</td>
</tr>
<tr>
<td>14.4</td>
<td>4/6</td>
<td>—</td>
</tr>
<tr>
<td>17.3</td>
<td>6/6</td>
<td>1/6</td>
</tr>
<tr>
<td>20.8</td>
<td>—</td>
<td>2/6</td>
</tr>
<tr>
<td>25.0</td>
<td>—</td>
<td>4/6</td>
</tr>
<tr>
<td>30.0</td>
<td>—</td>
<td>6/6</td>
</tr>
<tr>
<td>LD50</td>
<td>11.99</td>
<td>22.3</td>
</tr>
<tr>
<td>95% Confidence limits</td>
<td>± 1.19</td>
<td>± 1.15</td>
</tr>
</tbody>
</table>

* 300 mg/kg, ip.

Our results with pyrazole protection are comparable to those of Peterson et al. (1963) in which ethyl alcohol increased the LD50 for ethylene glycol in rats from 5.8 ml/kg to 10.5 ml/kg. The greater affinity of ethyl alcohol than ethylene glycol for alcohol dehydrogenase was thought to be the basis for protection in their experiments.

It is obvious that an agent which has as its basis of action a decrease in the metabolism of ethylene glycol would not be able to prevent the central nervous system toxicity of the compound. The central nervous system depression caused by glycols would still be present in the treated animals and the animals which succumbed following treatment may have died because of central depression.

The findings reported here lend further indirect support to the idea that a significant part of ethylene glycol toxicity is caused by metabolism of the parent compound by alcohol dehydrogenase to more toxic products.

Since both ethanol and ethylene glycol are central nervous system depressants, it is possible that protection by such a combination might be limited by a combined central toxicity. Additive toxicity might not be found with pyrazole therapy (Wilson and Bottiglieri, 1962). The duration of action of pyrazole is relatively long, and a single administration should provide inhibition of alcohol dehydrogenase for a period long enough to allow for the excretion of a large amount of the glycol before extensive metabolic alteration (Goldstein and Pal, 1971).
Pyrazole is a toxic chemical and causes damage in several organs in experimental animals (Goldstein and Pal, 1971). However, the compound and its congeners have been used in experimental studies in man, and use of such material on a one-time basis in life-threatening poisoning might be an acceptable risk (Blomstrand and Theorell, 1970). It is hoped that the preliminary observations reported here will stimulate further study.

REFERENCES

WEIL, C. S. (1952). Tables for convenient calculation of median-effective dose (LD50 or ED50) and instructions in their use. Biometrics 8, 249–263.

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