INHIBITION OF ETHANOL TOXICITY BY LYSINE OROTATE (ORL)

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Received 23 January 1970

1. Introduction

Toxic doses of ethanol (3 g/kg) caused increased RNAase activity in the plasma 60 min after an i.p. injection and reduced the amount of RNA in the pancreas of rats [1]. The nucleotides liberated are oxidized by the xanthine-oxidase-catalase system which also oxidizes ethanol [2–4]. Orotic acid partially protects against the drop in RNA caused by ethanol in the pancreas of the rat [2]. This paper reports investigations of a possible protection against ethanol toxicity by lysine orotate, a soluble form of orotic acid.

2. Methods

Lysine orotate at doses of 0.1, 1.0, 3.0, 10.0, 100.0, 300.0 and1000.0 mg/kg. respectively was injected (i.p.) one hour before ethanol into a group of eighty male Swiss albino mice. Ten animals served for each dose; a control group of ten received 0.9% NaCl one hour before the alcohol. The dose of ethanol injected (10 g/kg) was the well established median lethal dose of ethanol by sub-cutaneous injection in mice [5]. Solutions of both substances were made in 0.9% NaCl. The temperature of the animal room where the injections were made was 23°C ± 1.5. The LD_{50} of 10 g/kg was established at 23°C, and was significantly modified by external temperature fluctuations [5].

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3. Results

Fig. 1 shows a general protection by lysine orotate against ethanol toxicity. Each dose of the orotate injected one hour before the injection of the alcohol, except for the strongest of 1 g/kg, decreased the mortality well below 50%. There were no deaths in the group that received 3 mg/kg.

4. Discussion

It has previously been demonstrated that a small dose of ethanol (2.5 g/kg) given 24 hr prior to an injection of its LD_{50} dose considerably reduces the toxic effects of the latter. This protection is afforded by way of the adrenal glands [6]; hydrocortisone at 50 mg/kg, injected under the same conditions, gives protection by raising the level of liver alcohol dehydrogenase and also by stimulating RNA synthesis directly [6, 7]. It would seem that lysine orotate acts by activating the D-amino acid oxidases which reduce it to hydrogen peroxide in the presence of oxygen. This reduction involves the peroxidase and xanthine-oxidase-catalase systems. In forming a hydrogen acceptor complex, ethanol is oxidized more rapidly. However, the protection by acetyl-salicyclic acid (0.5 g/kg) injected i.p. one hour before the LD_{50} of methanol in mice is due to inhibition of the peroxidase systems (xanthine-oxidase, monoamino-oxidase) [8]. In view of the very high rate of ethanol oxidation in mice especially after lethal and toxic doses [9], the effect of orotate may be additive. This view of lysine orotate action is supported by the fact that ethanol, at acute toxic doses and also after prolonged ingestion and chronic intoxication, increases the amount of α-oxoglutaric acid in rats and in man, [10, 11].

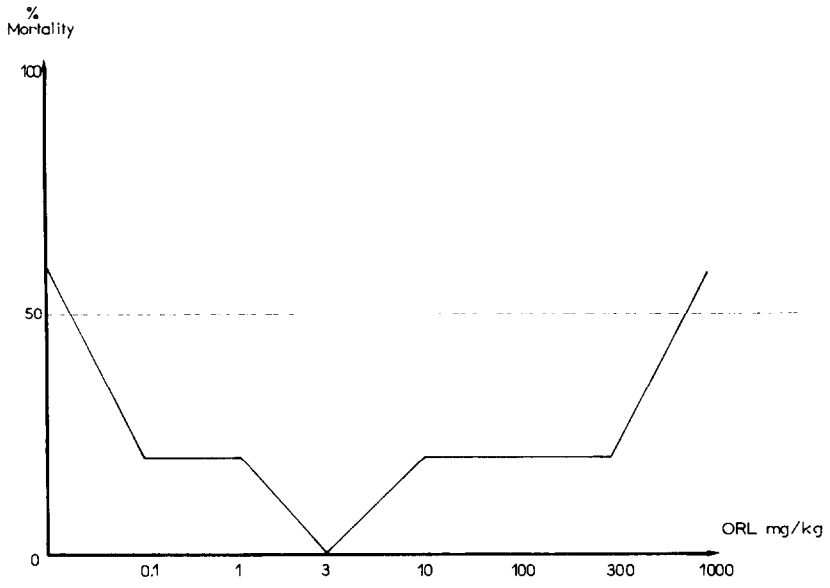

Fig. 1. 1 hour after ORL: C_2H_5OH at 10 g/kg.

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