COMPARATIVE PHARMACOLOGIC AND TOXICOLOGIC EFFECTS OF d-, l-, AND RACEMIC PROPYLENE GLYCOL

By

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SUMMARY

The d-, and l-optical isomers of propylene glycol have been investigated to determine if differences in pharmacologic or toxicologic activity exist. It has been found that l-propylene glycol produces a greater degree of central nervous system depression in mice and rats than does the d-optical isomer.

Evidence for this difference in depressant activity was provided when the results of sleeping time, anticonvulsant, and avoidance behavior studies were correlated with the disappearance rate and tissue distribution determinations of the individual isomers. The l-optical isomer of propylene glycol significantly increased the hypnosis induced by hexobarbital, while d-propylene glycol had no apparent effect. The protection afforded by l-propylene glycol against convulsive seizures was also much greater than that of d-propylene glycol, when mice were electrically stimulated. Finally, l-propylene glycol effected greater changes in rat behavior, indicative of central nervous system depression, than did d-propylene glycol. An explanation for the observed differences in depressant action was provided by the disappearance rate and tissue distribution studies, which revealed that the

d-optical isomer of propylene glycol disappeared from mice and rats much faster than l-propylene glycol, thus providing higher tissue levels of l-propylene glycol for longer periods of time.

In addition to differences in the level of depression induced by d-, and l-propylene glycol, a definite synergism with ethanol has been shown in sleeping time and activity studies. This synergistic ethanol-propylene glycol interaction can possibly be explained by the difference in the disappearance rate and in the tissue distribution of the drugs. A mutual metabolic inhibition resulted in increased tissue concentrations of both drugs, and a degree of central nervous system depression was attained, which would not have occurred from the addition of the depressant properties of both drugs.

A further indication of pharmacological differences among d-, and l-propylene glycol was also provided by the synergism with ethanol. The tissue distribution study demonstrated that in rats, ethanol will depress the disappearance of d-propylene glycol to a greater extent than the l-optical isomer, and d-propylene glycol will in turn, also reduce the disappearance rate of ethanol more than will the l-optical isomer. This evidence suggests an enzymatic pathway common to both ethanol and propylene glycol in rats which, moreover,

has a definite preference for d-propylene glycol rather than l-propylene glycol.

In contrast, the disappearance rate study in mice did not indicate that one optical isomer of propylene glycol was influencing the disappearance of ethanol to a different degree than the other, nor that ethanol affected the disappearance of the d-, and l-optical isomers differently. However, the same mutual inhibition of metabolism was evident, indicating a common enzymatic pathway. Since substantially larger quantities of ethanol were presented to the mice (4 g/kg) than to the rats (2 g/kg), a masking effect could have occurred. In addition, when the disappearance rate of racemic propylene glycol was compared to each of the optical isomers, it appears that the d-propylene glycol is depleted almost completely before the l-optical isomer is attacked, without any indication of competition between the two forms.

In the individual rat tissues concentrations of the optical isomers of propylene glycol and ethanol, alone or in combination, indicate that the kidney contained these drugs to almost the same degree as the blood, while the liver usually had lower concentrations. There is also some indication that d-propylene glycol, especially when in combination with ethanol, was more favorably received by this organ.

The proposed use of propylene glycol, particularly the d-optical isomer, as an ataractic agent in veterinary medicine (27) appears to be unwarranted. The data presented herein indicates that in the species tested, the suggested dosage is far too low to effect tranquilization, while d-propylene glycol exhibits central nervous system depression to a much lesser degree than does l-propylene glycol. However, without doubt, other animal species may react differently to these drugs, and further investigation is required in order to establish any true pharmacologic function that is not proximal to the toxicologic function.