Effects of 1,2-Propanediol on Blood Glucose and Liver Glycogen of Young Rats (34524)

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1, 2-Propanediol (propylene glycol) is extensively used as a vehicle in many pharmacological preparations (1, 2). This is because it has low toxicity (3) and because of its ability to dissolve many compounds not soluble in water. Ambrose (4) reported that administration of undiluted propylene glycol dipropionate (8 ml/kg) in rabbits did not produce any local or systemic reactions and concluded that within reason the ingestion or handling of propylene glycol does not involve any significant health hazards. Harvey *et al.* (5) reported that a single dose of propylene glycol as high as 7.5 mg/kg was well tolerated by the intravenous route in rats. Hickman (6) reported that the intraperitoneal (ip) administration of propylene glycol in mice resulted in the lack of coordination of movement followed by deep narcosis, but none of the mice died within 7 days of injection. In an earlier study, using weanling rats 50–60 g, it was noticed that propylene glycol as a carrier vehicle for phenylthiourea had produced an enormous increase in the blood glucose. This prompted us to study the effects of propylene glycol on blood glucose and liver glycogen in the weanlings in regard to the onset and duration of its effects on blood glucose and liver glycogen.

Propylene glycol behaves potentially as a carbohydrate in the metabolic pathway. It is glycogenic in starved rats (7) to an extent comparable to pyruvic acid (8); it has been used as a substitute for carbohydrate in the treatment of bovine ketosis (9). It is likely that a small amount of propylene glycol is readily metabolized via the lactate propanediol pathway (10) without causing any systemic metabolic upsets. The present report shows that a high nonlethal dose of propylene glycol is associated with severe disturbances in carbohydrate metabolism. Thus, the possible consequences of metabolic upsets caused by propylene glycol as such should be borne in mind while using it as a carrier vehicle for drugs.

Materials and Methods. Sprague-Dawley male rats weighing 50–60 g were used throughout the experiment. They were fed Purina rat chow and water *ad libitum*. The dose-response curve for lethality of propylene glycol was determined. Mortality was checked every 3 hr for a period of 12 hr and at 24 hr after administration of propylene glycol. The maximum tolerated dose (10 ml/kg) having no lethal effect was used in the subsequent metabolic studies.

One dose of propylene glycol (10 ml/kg) was administered ip. The control rats were injected with an equivalent amount of saline. The control and experimental rats were then transferred into metabolic cages in order to determine the food intake. The animals were decapitated at different times and blood samples were collected in heparinized tubes. Duplicate samples were run for each rat to measure the level of blood glucose according to the method of Krebs *et al.* (11, 12). For the determination of liver glycogen, a piece of liver was removed immediately after decapitation, weighed quickly, and transferred into a test tube containing hot 30% KOH. Liver glycogen was measured according to the method of Hensen *et al.* (13). The determination of blood glucose and liver glycogen at any time interval after propylene glycol treatment was done simultaneously with a saline control.

In order to judge the capacity of animals to synthesize liver glycogen after propylene

TABLE I. Toxicity of Propylene Glycol (PG) in Sprague-Dawley Male Rats Weighing 50–60 g.

Mortality	Dose of PG (ml/kg) ip				
	10	15	20	25	30
Number of deaths/number of animals used	0/50	1/10	7/10	9/10	8/10

glycol treatment, the experiments were carried out as follows: Rats were injected with propylene glycol (10 ml/kg) ip. The control rats received at the same time an equivalent amount of saline. Soon after injection they were transferred into separate cages, where they had access to water *ad libitum*, but not to food. Six hours after the administration of propylene glycol or saline, a 10% dextrose solution was injected ip hourly for 6 hr to provide 50 mg of dextrose/hr/rat in one series of experiments and 100 mg of dextrose in the second series. Thereafter, the determination of liver glycogen was performed as described previously.

Data are reported in terms of average values with their standard error of mean (SE). The Student *t* test was applied to test the significance of differences between means.

Results and Discussion. The maximum nonlethal dose of propylene glycol by the intraperitoneal route was found to be 10 ml/kg in the young rats. This dose caused a mild central nervous system (CNS) depression which lasted for 2 or 3 hr. The minimum lethal dose was 15 ml/kg, and the dose producing the lethal effect close to LD_{100} was between 25 and 30 ml/kg (Table I). Death in all cases of propylene glycol toxicity resulted from a severe CNS depression and respiratory failure.

Propylene glycol at the dose of 10 ml/kg seems to have a biphasic effect on the blood glucose level. A marked increase in blood glucose occurred after 15 min with a maximum increase after 1½ hr. The increase in blood glucose lasted for a period of 6 hr. Thereafter, a slight decrease at the 12-hr interval was noticed. However, the significance of the decrease at 12 hr is questionable since these values fall within a broad normal range (Table II). The liver glycogen content in rats treated with propylene glycol or with saline was just about the same for a period of 6 hr (Table II). This indicated strongly that the increase in the blood glucose level after propylene glycol is not mediated through the mobilization of liver glycogen, but that propylene glycol itself is a direct precursor of blood glucose. This is in agreement with the work of Emery *et al.* (14) that intraruminal administration of propylene glycol in the cow was glucogenic in the classical sense of that term, namely, that it is metabolized via intermediates and leads to net synthesis of glucose.

A consistent depletion of liver glycogen was noticed 12 hr after propylene glycol administration (Table II). This depletion could possibly be accounted for by a reduced food intake, as the propylene glycol-treated rats during the day consumed only one half the amount of food in 12 hr as the control group (Table II). However, food consumption by propylene glycol-treated rats during the night in 12 hr was twice as much as during the day (Table II), and, because of diurnal variation in the food intake, practically no difference in the liver glycogen content was observed. This suggested the possibility that the rats treated with propylene glycol somehow lack the ability to synthesize the liver glycogen. This was substantiated in the following experiment: Rats, 6 hr after propylene glycol treatment, when subjected to 100 mg of dextrose ip hourly for 6 hr, showed a profound depression in their ability to synthesize liver glycogen. The livers of control saline-treated rats under the identical conditions, contained three times more liver glycogen than those of the rats treated with propylene glycol (Table III).

The actual mechanism as how propylene glycol (10 ml/kg) administration decreases the liver glycogen content is not clear at the present. Such possibilities as the inhibition of glycogen synthetase due to a high amount of glucose resulting from propylene glycol or

TABLE II. Effect of a Single Dose (10 ml/kg) of Propylene Glycol (PG) on Blood Glucose, Liver Glycogen, and Food Intake at Different Times in Young Rats.

Time after PG-administration (hr)	Glucose (mg/100 ml of blood, avg ± SE)		Glycogen (% of liver weight, avg ± SE)		Food intake (g/rat, avg ± SE)	
	Control	Propylene glycol	Control	Propylene glycol	Control	Propylene glycol
0.25	129.2 ± 3.88 (5)	182.4 ± 5.21[a] (5)	4.18 ± 0.24 (5)	3.75 ± 0.65 (5)	0.0	0.0
1.5	131 ± 2.66 (5)	245.3 ± 11.55[a] (5)	3.30 ± 0.43 (5)	2.47 ± 0.35 (5)	0.0	0.0
3.0	120.9 ± 9.25 (16)	180.2 ± 14.74[b] (9)	3.59 ± 0.79 (13)	4.50 ± 0.72 (7)	0.0	0.0
6.0	121.4 ± 6.68 (5)	188.2 ± 15.20[b] (5)	3.01 ± 0.29 (5)	2.95 ± 0.32 (5)	0.0	0.0
12.0[c]	134.0 ± 2.77 (5)	117.0 ± 6.04[d] (5)	3.61 ± 0.39 (5)	1.61 ± 0.34[b] (5)	2.23 ± 0.18 (4)	1.05 ± 0.26 (5)
12.0[e]	134.0 ± 2.39 (5)	119.3 ± 5.65[d] (5)	5.17 ± 0.34 (5)	1.54 ± 0.22[a] (5)	7.30 ± 0.46 (4)	2.53 ± 0.67 (4)

The figures in parentheses are the number of animals used.

[a,b,d] t values between propylene glycol and control saline are significant at 0.1%, 1%, and 5% level, respectively.

[c] Propylene glycol was injected at 8:00 AM; blood glucose and liver glycogen were determined on the same day at 8:00 PM.

[e] Propylene glycol was injected at 8:00 PM; blood glucose and liver glycogen were determined on the next day at 8:00 AM.

the CNS-depressant effect of propylene glycol (15) as such might well be involved, remain to be tested. However, the possibility of such factors as hypertonicity in the intraperitoneal cavity or pain from glycol irritation influencing the metabolic balance of young rats cannot be ignored.

Summary. The administration of a high nonlethal dose of propylene glycol (10 ml/kg) was found to affect the carbohydrate metabolism of young rats. There was a marked increase in the blood glucose in 15 min, with the maximum increase in 1½ hr; the overall increase in blood glucose lasted for a period of 6 hr. The amount of liver glycogen in propylene glycol and saline control was the same for 6 hr. A severe depletion in the liver glycogen was noticed 12 hr after propylene glycol treatment. Evidence has been provided that the rats treated with a high dose of propylene glycol have a drastically reduced capacity to synthesize or to store liver glycogen. Some of the possible mechanisms for the inhibitory effects of propylene glycol on synthesis of liver glycogen have been discussed. The present work provides the proof for the metabolic upsets associated with a large dose of propylene glycol used either as such or as a carrier vehicle in a drug study.

TABLE III. Effect of a Single Dose (10 ml/kg) of Propylene Glycol (PG) on Synthesis of Liver Glycogen in Young Rats.[a]

Treatment	No. of animals	Glucose (mg)	Glycogen (% of liver wt, avg ± SE)
Saline control	4	50	0.638 ± 0.115
Propylene glycol	4	50	0.537 ± 0.132
Saline control	4	100	3.620 ± 0.680[b]
Propylene glycol	6	100	1.23 ± 0.174[b]

[a] Design of the experiment is discussed in the Methods section.

[b] A t value between PG and saline control is significant at the 1% level.

This research was supported by a grant (GRS69-20) from the University of California, Davis. We highly appreciate the technical assistance given by Miss Susan Rice and Mrs. Sandra Goldbar.

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Received Sept. 8, 1969. P.S.E.B.M., 1970, Vol. 133.