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A SYSTEMATIC TREATMENT FOR ETHYLENE GLYCOL TOXICITY IN DOGS

by

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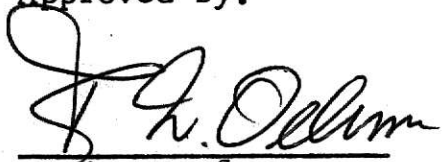

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INTRODUCTION

Ethylene glycol (EG) is used in industry as a solvent, but its main use is as a "permanent type" of automobile antifreeze (16). It is also used as a circulant coolant in the lunar and other modules developed for the space exploration programs (15). This is because of its high boiling point (197.5°C) and low cost.

Ethylene glycol toxicity has occurred in man and several species of animals for many decades (5,15,23,28). The toxicity has usually been accidental in man due to its ingestion as a cheap substitute for ethanol. Animals have also consumed it frequently, probably due to its sweet taste. The earliest reports of toxicity in dogs and cats in the United States were in 1951 (10) and 1955 (7). Toxicity has recently been reported in swine (20).

The biotransformation of EG and the physiopathology of toxicity has been a subject of numerous studies. It was long believed that the only metabolite responsible for the toxic actions of EG was oxalic acid (17), a potent nephrotoxic agent. However, it was recently demostrated that the liver enzyme alcohol dehydrogenase oxidizes EG to the following series of intermediary metabolites: glycolaldehyde, glycollic acid and glyoxylic acid. Only 3% or less of the glyoxylic acid is degradated to oxalic acid; the remainder is eliminated as respiratory carbon dioxide and glycine (6,15,26).

It has been suggested that death in acute cases of EG toxicity is due to a metabolic acidosis produced by the biotransformation process, or as a result of one or more of the metabolites (4,18), rather than due to the EG itself or the oxalic acid. Definitive identification of the acutely toxic component has not yet been accomplished (15,18), but glyoxylic acid has been shown to be the most probable agent (1).

The minimal lethal dose of EG in dogs had been reported as 6.6 ml. EG/kg. body weight (13). Death has also been reported with dosages of 4.4 ml. EG/kg. body weight (2). In both cases EG was administered orally as a substitute for water to moisten the dry feed. Four and two-tenth ml. EG/kg. body weight has also been reported to cause death in dogs (11). The route of administration in this instance was not mentioned.

The clinical signs of acute EG toxicity are: constant emesis, ataxia followed by depression, infrequent excitement 30 to 60 minutes after ingestion, weakness, progressive paresis, coma, convulsions, and death after 8 to 40 hours. Chronic toxicity results from survival through the acute stage, deposition of oxalate salts in the renal tubules, and death due to renal failure and uremia (2,7,11,12,13).

Since alcohol dehydrogenase exhibits distinctive substrate specificity (26), a rational basis for EG therapy was suggested using ethanol, a natural substrate for the enzyme (21,26). This

compound limits EG biotransformation by competitive inhibition and allows the EG to be excreted unchanged in the urine. Sodium bicarbonate has been shown to increase sodium and citrate excretion in the urine and favors urine alkalosis, thus reducing oxalate salt formation (2,3).

While there have been successful reports in the veterinary literature of the experimental use of ethanol as an antidote, treatment in all cases was started no later than 1 hour after poisoning and either sublethal or extremely high doses were used (2,18). It is unlikely that veterinarians in private practice would see a poisoned animal only one hour after ingestion. Thus this study was undertaken to determine: (1) the optimal ratios, doses and concentrations of the treatment components; (2) the EG doses at which successful antidotal therapy could still be achieved; and (3) the maximum length of time after poisoning at which ethanol could still effectively inhibit EG oxidation and produce clinical recovery.

MATERIALS AND METHODS

Thirty-five adult dogs of either sex, 23 beagles and 12 of mixed-breeding, were used. Their mean weight was 10.6 ± 0.43 (S.E.$\bar{x}$) kg. The beagles were raised in the laboratory's research colony and the mixed stock were secured from the local pound. A commercial dry dog food[a] and water were offered _at libitum_. Ani-

---

[a] Golden Choice Dog Meal, Coors Company, Golden, Colo.

mals were stabilized for at least one week before experimentation.

Twenty-four hours before dosing the dogs were placed in individual metabolic cages to facilitate urine collection and were offered water free-choice throughout the experiment. EG[b] was administered by stomach tube as a 50% aqueous solution after 24 hours of fasting. To avoid vomiting and to ease handling, all dogs were injected intravenously with 1 mg. chlorpromazine hydrochloride[c]/kg. body weight one-half hour before dosing. Feeding was reestablished 48 hours after dosing.

Since previous studies had shown varying responses to different treatments and dosages,[d,e] a pilot study was conducted in 6 dogs to determine the appropriate concentration and dose of ethanol and to evaluate whether or not an alkalinizing agent, such as sodium bicarbonate should also be administered. An intravenous dose of 5.5 ml. 20% ethanol in physiological saline/kg. body weight was found most effective. The intraperitoneal administration of 8.0 ml. 5% sodium bicarbonate in physiological saline/kg. was also

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[b] Ethylene Glycol, Analytical Reagent, Mallinckrodt Chemical, St. Louis, Mo.

[c] Thorazine, Pitman-Moore, Indianapolis, Ind.

[d] Walker, W., and Oehme, F. W., Comparative Toxicology Laboratory, Kansas State University, Manhattan, Ks.: Unpublished data, 1970.

[e] Fabianke, C., and Oehme, F. W., Comparative Toxicology Laboratory, Kansas State University, Manhattan, Ks.: Unpublished data, 1971.

useful and was incorporated in the treatment system. Treatments of ethanol and sodium bicarbonate were given initially and repeated every 4 hours for 4 treatments and then every 6 hours for 4 more treatments. The complete treatment schedule covered approximately 40 hours following initiation.

The 29 remaining dogs were divided into control and treated groups and handled in the following manner: Four dogs were dosed with 10 ml. EG/kg. body weight; 1 received no treatment and 3 received initial treatment 1 hour post-dosing. Thirteen dogs were dosed with 8 ml. EG/kg. body weight; 4 received no treatment, 5 received initial treatment 2 hours post-dosing and 4 received initial treatment 4 hours post-dosing. Twelve dogs were dosed with 6 ml. EG/kg. body weight; 4 received no treatment, 4 received initial treatment 4 hours post-dosing and 4 received initial treatment 6 hours post-dosing.

Ethylene glycol plasma concentrations were determined by the method of Harger and Forney (8) on heparinized blood samples collected at 0, 1, 3, 6, 9, 12, 24, 48, 72, 96, 168, and 240 hours after dosing. Blood pH was determined under the same schedule within 5 minutes of collection using a Corning expanded scale pH meter with a combination micro-electrode. Blood urea nitrogen (BUN) was evaluated at 0, 12, 24, 48, 72, 96, 168, and 240 hours by the Charneys and Marback method (9).

Urine total volume, specific gravity and sediment exami-

nation were determined at 0, 24, 48, and 72 hours after dosing. Urine concentration of EG was quantitated by the Harger and Forney method (8) at the same time intervals after dosing. From these values the urinary excretion of EG was calculated for the first 72 hours after dosing.

Any animals dying during the experiment were necropsied within 30 minutes after death. Terminal plasma and urine samples were collected and evaluated for EG content by the methods previously described. Animals that survived 240 hours, but having BUN levels in excess of 100 mg./100 ml., were permitted to die from terminal uremia. Other dogs were euthanatized between 240 and 288 hours post-dosing, even though in most cases BUN values were within the normal range and clinical evaluation revealed the animal to be in good condition. Kidney, lung, liver, stomach, intestine, cerebrum and cerebellum tissues were fixed in buffered neutral 10% formalin, embedded in paraffin, sectioned at 6 μ and stained with hematoxylin-eosin. Finished sections were observed under normal and polarized light.

The results of all treatments and examinations were tabulated for each group and subjected to statistical analysis using an unequal subclass least square analysis of variance computer program, which was run on an IBM 360/50 computer. Least significant differences and analysis of variance employing 95% confidence levels were used in most cases (24).

RESULTS

Survival Rates

Survival rates were directly related to the dose of EG administered and the length of time elapsed following dosing before the treatment regimen was initiated (Fig. 1). High EG dosage rates and increasing time intervals between dosing and treatment resulted in poor rates of survival.

All 4 dogs receiving 10 ml. EG/kg. body weight died. The control dog died 12 hours after dosing and 2 of the treated dogs died 15 and 22 hours post-dosing. The remaining treated dog lived 312 hours, but died from renal failure and uremia. However, this animal vomited 2 hours after dosing and 4.8 ml. EG were determined to be in the vomitus. This animal thus retained a dose of 9.6 ml. EG/kg. body weight.

All 4 control dogs receiving 8 ml. EG/kg. body weight died. The mean survival time was 20.0 ± 5.21 hours. Three of the 5 dogs treated 2 hours after dosing survived. One dog died 77 hours post-dosing and the other died 336 hours post-dosing from renal failure and uremia. All 4 dogs treated 4 hours after dosing died. Their mean survival time was 27.2 ± 2.77 hours.

The 4 control dogs receiving 6 ml. EG/kg. body weight died. The mean survival time was 28.0 ± 5.12 hours. Three of the 4 dogs treated 4 hours after dosing survived. The dog that died survived 264 hours and suffered from renal failure and uremia. Two

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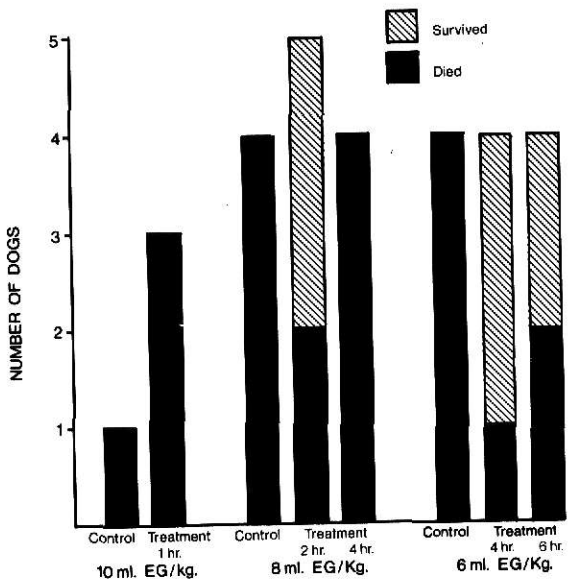

Fig. 1--Clinical effect of EG dosage rates and treatment initiated at various post-dosing times.

of the 4 dogs treated initially 6 hours after dosing survived. The remaining 2 dogs died 18 and 99 hours post-dosing.

Clinical Signs

All dogs, whether treated or not, showed initial clinical signs of apprehension, moderate depression and mild ataxia 30 to 60 minutes post-dosing. These signs were not sufficiently severe to always be noticed by the casual observer. Vomiting was seen only in a dog receiving 10 ml. EG/kg. body weight. Progressive depression, incoordination, ataxia followed by paresis, and coma were commonly seen. The dogs developed coma 6 to 12 hours post-dosing, depending upon the dosage rate administered, those dogs receiving the higher dose developing coma earlier. Convulsions were not seen in any of the control dogs.

Administration of the ethanol treatment produced an anesthesic-like state in all treated animals. This state lasted 2½ to 4 hours following the first few treatments, but during later treatments the dogs awaken from the treatment at increasing rates. They recovered from the anesthesia more quickly and were conscious during the majority of the period between the later treatments.

The dogs exhibited marked thirst and drank water immediately upon regarding consciousness. Limiting access to frequent small water volumes reduced the incidence of vomiting.

The dogs receiving 10 or 8 ml. EG/kg. body weight and respectively treated 1 or 4 hours post-dosing never recovered from

the anesthesic-like state that followed the first treatment. Other treated dogs were able to walk with some difficulty after the third or fourth treatment, but the control dogs progressed with severe acidosis to coma and death.

All treated animals surviving 48 hours consumed food, but those with increased BUN levels began vomiting and thereafter deteriorate very rapidly. Progressive increases in the BUN levels paralleled the clinical signs of renal failure and uremia. Acidosis, stomatitis, diarrhea and convulsions were the terminal stages of this renal syndrome.

Plasma Ethylene Glycol Concentrations

Mean values for plasma EG concentrations are given in Table 1. For all dogs, with or without treatment, plasma EG levels rose rapidly in 1 hour and reached maximal values 3 hours post-dosing. These levels decreased after 24 hours and approached non-detectable limits 48 hours post-dosing.

Plasma values of EG from dogs receiving 10 ml. EG/kg. body weight were higher ($P<0.1$), than those receiving 8 ml. EG/kg. body weight. The dogs receiving the 10 ml./kg. dose also had higher plasma EG values than those receiving 6 ml. EG/kg. body weight, but these differences were not statistically significant. There were no statistical differences between the plasma EG levels of dogs receiving 8 ml. and those receiving 6 ml. EG/kg. body weight.

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Ethylene Glycol at Various Doses. Means as mg./100 ml. (± Standard Error)

body weight		6 ml./kg. body weight		
Treatment		Control	Treatment	
at 2 hours	at 4 hours		at 4 hours	at 6 hours
5	4	4	4	4
1.20 (0.90)	0.80 (0.50)	3.30 (1.50)	4.00 (1.40)	3.00 (1.00)
1300.00 (224.00)	737.00 (112.00)	1187.00 (171.00)	1187.00 (251.00)	1125.00 (222.00)
1410.00 (300.00)	962.00 (62.00)	1562.00 (97.00)	1737.00 (336.00)	1575.00 (224.00)
1470.00 (250.00)	1037.00 (144.00)	1262.00 (111.00)	1650.00 (306.00)	1225.00 (215.00)
1260.00 (280.00)	925.00 (124.00)	1075.00 (187.00)	1375.00 (172.00)	1150.00 (183.00)
1130.00 (265.00)	775.00 (124.00)	850.00 (106.00)	1125.00 (222.00)	1112.00 (215.00)
940.00 (260.00)	662.00 (111.00)	737.00 (111.00)	775.00 (112.00)	962.00 (214.00)
74.00 (22.00)	1150.00+ (212.00)	1075.00+ (371.00)	49.00 (9.20)	472.00** (2.82)
8.90 (3.00)	--- ---	--- ---	20.70 (4.80)	24.00** (14.00)
5.60 (2.10)	--- ---	--- ---	6.30 (1.60)	19.00** (10.00)
2.00* (1.10)	--- ---	--- ---	4.00 (0.90)	21.00** (13.00)
1.20* (0.60)	--- ---	--- ---	1.90 (1.10)	1.30+ (0.80)

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TABLE 1--Mean Ethylene Glycol Plasma Concentrations of Dogs Receiving

	10 ml./kg. body weight		8 ml./kg.
	Control	Treatment at 1 hour	Control
No. of animals	1	3	4
Hours after administration			
0	0.0 ---	17.80 (00.68)	17.80 (8.70)
1	1450.0 ---	1466.00 (295.00)	962.00 (233.00)
3	1500.0 ---	1766.00 (224.00)	1462.00 (215.00)
6	1750.0 ---	1983.00 (95.00)	1387.00 (249.00)
9	1200.0 ---	1766.00 (153.00)	1150.00 (250.00)
12	1200.0 ---	1616.00 (196.00)	1200.00** (248.00)
24	--- ---	1566.00 (95.00)	1150.00+ (106.00)
48	--- ---	134.00++ ---	1150.00+ (212.00)
72	--- ---	22.50++ ---	--- ---
96	--- ---	16.00++ ---	--- ---
168	--- ---	8.50++ ---	--- ---
240	--- ---	8.50++ ---	--- ---

* 4 animals
** 3 animals
\+ 2 animals
++ 1 animal

The control dogs receiving 8 ml. EG/kg. body weight had higher plasma EG values than those treated 2 and 4 hours post-dosing. The differences were statistically significant ($P<0.05$). Plasma EG values of dogs treated 2 hours post-dosing were also higher than those treated 4 hours post-dosing. This difference was also statistically significant ($P<0.05$).

There were no statistical differences between the plasma EG values of the control and treated dogs receiving 6 ml. EG/kg. body weight.

Blood pH

Mean blood pH values for all animals are given in Table 2. Blood pH values for control animals were consistenly lower than for the treated dogs ($P<0.05$).

The control dogs receiving 8 ml. EG/kg. body weight had lower blood pH values than those treated 2 and 4 hours post-dosing. The dogs treated 4 hours post-dosing had lower blood pH values than those treated 2 hours post-dosing. All differences were significant ($P<0.05$).

The control dogs receiving 6 ml. EG/kg. body weight had lower blood pH values than those treated 4 and 6 hours post-dosing, but dogs treated 6 hours post-dosing had lower blood pH values than those treated 4 hours post-dosing. The differences were statistically significant ($P<0.05$).

TABLE 2--Mean Whole Blood pH Values of Dogs Receiving Ethylene Glycol at Various Doses. Means as ± "0 Hour" (± Standard Error)

	10 ml./kg. body weight		8 ml./kg. body weight			6 ml./kg. body weight		
	Control	Treatment at 1 hour	Control	Treatment at 2 hours	Treatment at 4 hours	Control	Treatment at 4 hours	Treatment at 6 hours
No. of animals	1	3	4	5	4	4	4	4
Hours after administration								
0	7.51 ---	7.55 (0.005)	7.55 (0.004)	7.56 (0.019)	7.52 (0.007)	7.53 (0.008)	7.55 (0.007)	7.54 (0.01)
1	-0.03 ---	-0.036 (0.015)	-0.035 (0.0103)	-0.028 (0.013)	-0.025 (0.007)	-0.05 (0.01)	-0.037 (0.005)	-0.037 (0.007)
3	-0.26 ---	-0.046 (0.003)	-0.162 (0.011)	-0.04 (0.015)	-0.112 (0.018)	-0.12 (0.007)	-0.10 (0.010)	-0.13 (0.027)
6	-0.51 ---	-0.0066 (0.028)	-0.35 (0.055)	+0.004 (0.033)	-0.092 (0.014)	-0.17 (0.034)	-0.08 (0.023)	-0.22 (0.07)
9	-0.75 ---	-0.033 (0.033)	-0.36** (0.018)	+0.024 (0.0228)	-0.050 (0.0197)	-0.29 (0.05)	-0.32 (0.014)	-0.15 (0.034)
12	-0.88 ---	+0.065 (0.0035)	-0.39+ (0.018)	-0.002 (0.014)	-0.010 (0.020)	-0.37 (0.058)	-0.002 (0.008)	-0.10 (0.03)
24	--- ---	0.0++ ---	-0.57+ (0.10)	+0.04 (0.019)	+0.016** (0.035)	-0.56+ (0.14)	+0.002 (0.015)	+0.006** (0.007)
48	--- ---	+0.02++ ---	--- ---	-0.014 (0.010)	--- ---	--- ---	+0.022 (0.011)	+0.013** (0.011)
72	--- ---	-0.08++ ---	--- ---	-0.022 (0.016)	--- ---	--- ---	+0.017 (0.016)	-0.013** (0.022)
96	--- ---	-0.11++ ---	--- ---	-0.031 (0.008)	--- ---	--- ---	-0.020 (0.015)	-0.013** (0.033)
168	--- ---	-0.14++ ---	--- ---	-0.062* (0.015)	--- ---	--- ---	-0.035 (0.016)	-0.010+ (0.014)
240	--- ---	-0.13++ ---	--- ---	-0.020* (0.024)	--- ---	--- ---	-0.027 (0.014)	-0.020+ (0.014)

* 4 animals
** 3 animals
\+ 2 animals
++ 1 animal

Blood Urea Nitrogen Levels

Mean BUN values are given in Table 3. The dogs receiving 8 ml. EG/kg. body weight had significantly increased BUN values 12 and 24 hours post-dosing ($P<0.05$). However, the dogs treated 2 hours post-dosing had significantly lower BUN values than the control dogs or those treated 4 hours post-dosing ($P<0.05$).

The control dogs receiving 6 ml. EG/kg. body weight and those receiving the same dose and treated 6 hours post-dosing had higher BUN values than dogs treated 4 hours post-dosing with the 6 ml./kg. dose ($P<0.05$).

The BUN levels in all surviving animals returned to within normal range 72 to 96 hours post-dosing. However, the BUN values in dogs that died continued to increase until death.

Urine Analyses

Mean urine volume and specific gravity are given in Table 4. The EG dosage levels administered did not affect the urine volume or the specific gravity during the first 24 hours. However, urine volume was higher in all dogs during the first 24 hours than during the 48 and 72 hour post-dosing period.

The urine volume of dogs receiving 6 ml. EG/kg. body weight and treated 4 hours post-dosing was higher than those treated 6 hours post-dosing ($P<0.1$). The urine specific gravity of dogs in the same dosage group treated 4 hours post-dosing was signifi-

TABLE 3--Mean Blood Urea Nitrogen of Dogs Receiving Ethylene Glycol at Various Doses. Means as mg./100 ml. (± Standard Error)

	10 ml./kg. body weight		8 ml./kg. body weight			6 ml./kg. body weight		
	Control	Treatment at 1 hour	Control	Treatment at 2 hours	Treatment at 4 hours	Control	Treatment at 4 hours	Treatment at 6 hours
No. of animals	1	3	4	5	4	4	4	4
TIME (hours)								
0	9.5	9.11	10.75	8.43	11.97	13.97	8.4	11.65
	---	(0.15)	(1.87)	(0.65)	(1.49)	(1.25)	(0.29)	(1.28)
12	33.4	12.4**	24.0+	10.02	22.35	28.92	10.07	20.30
	---	(0.45)	(2.12)	(0.85)	(2.94)	(3.16)	(0.05)	(3.69)
24	---	25.30+	61.75+	12.74	45.4**	63.5+	17.02	38.10**
	---	(8.34)	(9.30)	(1.01)	(18.62)	(0.35)	(1.82)	(13.70)
48	---	14.3++	---	15.38	---	86.0++	12.27	50.83
	---	---	---	(2.30)	---	---	(2.39)	(26.62)
72	---	69.0++	---	35.94	---	---	23.27	66.76
	---	---	---	(15.55)	---	---	(11.06)	(41.88)
96	---	112.0++	---	28.47*	---	---	39.31	68.06
	---	---	---	(15.75)	---	---	(22.22)	(43.67)
168	---	213.0++	---	33.65*	---	---	64.00	13.25+
	---	---	---	(20.02)	---	---	(37.82)	(2.23)
240[a]	---	248.0++	---	38.65*	---	---	91.82	14.80+
	---	---	---	(26.37)	---	---	(64.47)	(0.71)
240[b]	---	---	---	8.2**	---	---	17.43**	14.80+
	---	---	---	(0.46)	---	---	(3.34)	(0.71)

a--Including animal that survived more than 240 hours.
b--Including animals that actually survived.

* 4 animals + 2 animals
** 3 animals ++ 1 animal

Ethylene Glycol at Various Doses. Means as ml. (± Standard Error)

body weight			6 ml./kg. body weight					
Treatment hours	at 4 hours		Control		Treatment at 4 hours		at 6 hours	
	4		4		4		4	
	72.47 (5.39)		47.77 (8.86)		68.82 (2.56)		70.17 (8.05)	
USG	UV	USG	UV	USG	UV	USG	UV	USG
1.030 (0.03)	67.0++ ---	1.040++ ---	65.3** (2.4)	1.035** (0.02)	171.2 (43.9)	1.039 (0.008)	68.3** (29.5)	1.028** (0.03)
1.016 (0.013)	1039.0 (71.4)	1.014 (0.017)	621.2 (101.5)	1.014 (0.007)	1163.7 (138.2)	1.015 (0.008)	12.4 (27.3)	1.014 (0.015)
1.017 (0.018)	95.0++ ---	--- ---	50.0+ ---	--- ---	330.0 (73.8)	1.022 (0.021)	538.3** (66.8)	1.014** (0.016)
1.009 (0.01)	--- ---	--- ---	--- ---	--- ---	390.0 (48.9)	1.026 (0.028)	780.7** (24.4)	1.013** (0.012)

TABLE 4--Mean Urine Volume and Urine Specific Gravity of Dogs Receiving

	10 ml./kg. body weight						8 ml./kg.
	Control		Treatment at 1 hour		Control		at 2
No. of animals	1		3		4		5
EG Adm. (ml.)	128.00		119.60		79.50		71.12
	---		(3.14)		(10.15)		(3.48)
TIME (hours)	UV	USG	UV	USG	UV	USG	UV
0	---	---	415.0+	1.022+	270.0++	1.022++	116.0
	---	---	(144.9)	(0.040)	---	---	(39.2)
24	408	1.015	1316.0	1.012	841.2	1.013	980.0
	---	---	(99.0)	(0.003)	(73.1)	(0.015)	(67.7)
48	---	---	405.0++	1.020++	50.0++	1.018++	813.0
	---	---	---	---	---	---	(130.8)
72	---	---	550.0++	1.018++	---	---	819.0
	---	---	---	---	---	---	(79.7)

UV---Urine volume
USG--Urine specific gravity

* 4 animals
** 3 animals
\+ 2 animals
++ 1 animal

cantly higher than those treated 6 hours post-dosing ($P<0.05$).

Oxalate crystals were seen in the urinary sediment of all dogs as early as 4 to 6 hours post-dosing. The size and number of crystals were greater in the control dogs and in those treated several hours after dosing. Numerous oxalate crystals remained in the sediment of the control dogs until death. In the treated dogs the oxalate crystals either disappeared or were minimal during the recovery period.

Urinary EG Recovery Rates

Mean EG volumes recovered in the urine are given in Table 5. Elimination of EG in the urine at all dosage and treatment levels during the first 24 hours was not statistically different.

The percent administered EG recovered in the surviving animals ranged from 23 to 83% during the 72 hour period of observation, with the recovery percent ranging from 9.4 to 45.4% during the first 24 hours. The percent of administered EG recovered during the first 24 hours in the urine of the control dogs ranged only from 5.7 to 23.4%. Fig. 2 is a visual presentation of the EG recovery in the urine from dogs receiving 6 ml. EG/kg. body weight.

Necropsy Findings

Gross necropsy lesions commonly seen were pulmonary edema, acute congestion of all body tissues, and various degrees of di-

TABLE 5--Mean Ethylene Glycol Eliminated in Urine of Dogs Receiving Ethylene Glycol at Various Doses.. Means as Cumulative ml. (± Standard Error)

	10 ml./kg. body weight		8 ml./kg. body weight			6 ml./kg. body weight		
	Control	Treatment at 1 hour	Control	Treatment at 2 hours	Treatment at 4 hours	Control	Treatment 4 hours	Treatment 6 hours
No. of animals	1	3	4	5	4	4	4	4
TIME (hours)								
0	--- ---	0.13+ (0.007)	0.33++ ---	0.58 (0.013)	0.04++ ---	0.05** (0.005)	0.081 (0.016)	0.03** (0.009)
24	6.023 ---	34.89* (4.78)	14.94* (2.99)	20.43 (4.70)	20.13* (3.81)	12.86* (3.01)	28.17 (6.14)	27.74 (2.00)
48	--- ---	49.74++ ---	18.86++ ---	33.35 (7.21)	30.77++ ---	18.00+ (4.03)	34.09 (5.17)	37.45** (4.21)
72	--- ---	63.13++ ---	--- ---	36.07 (7.87)	--- ---	--- ---	39.13 (5.67)	45.58** (7.33)
% Dose Recovered	4.70 ---	34.56 (8.62)	21.93 (6.11)	50.62 (11.29)	28.07 (5.33)	28.11 (4.20)	56.41 (7.02)	62.90** (13.58)

* 4 animals
** 3 animals
\+ 2 animals
++ 1 animal

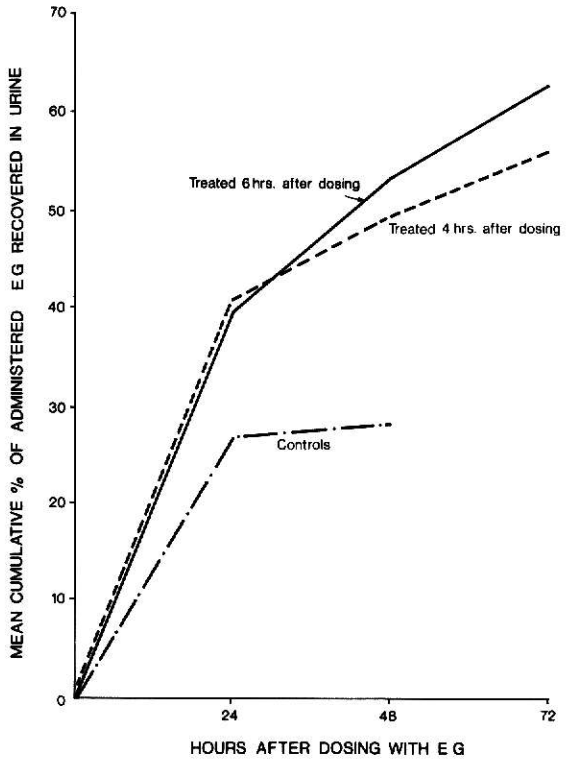

Fig. 2--Mean Recovery Rates of EG. Urine from dogs receiving 6 ml. EG/kg. body weight. Values are cumulative percent of administered EG recovered.

gestive tract hyperemia. The meninges, cerebrum, cerebellum and brain stem did not have gross pathological changes. The kidneys were swollen, but no other visible changes were observed.

The animals that died from renal failure and uremia were dehydrated, exhibited weight loss and had oral ulcerations and hemorrhagic gastritis. The kidney was the organ primarily affected with microscopic changes. The presence of oxalate crystals was the singular most characteristic finding in all control dogs (Fig. 3). The crystals were readily seen with ordinary light, but were much better appreciated with polarized light. They were chiefly localized in the proximal tubules. However, due to tubular epithelium damage it was difficult to deny the presence of oxalate crystals in the distal tubules also.

The treated dogs dying 15 to 36 hours post-dosing had no or few oxalate crystals scattered throughout the kidney, while 2 dogs that died 77 and 99 hours post-dosing had numerous oxalate crystals. Dogs that died from renal failure and uremia had numerous cystic tubules in addition to the oxalate crystals (Fig. 4).

Typical kidney lesions of EG toxicity included congestion, large numbers of proteinaceous casts, and a varying degree of tubular damage. Tubular damage was related to the length of survival following dosing and ranged from hydropic degeneration to frank tubular necrosis with karyorrhexis, pyknotic nuclei, dis-

Fig. 3--Kidney of a control dog receiving 8 ml. EG/kg. body weight, showing numerous oxalate crystals in the tubules (arrows). H&E stain; x 40.

Fig. 4--Kidney of a dog receiving 8 ml. EG/kg. body weight and treated 2 hours post-dosing. Died 336 hours post-dosing, showing flattened epithelium and cystic tubules. H&E stain; x 40.

rupted tubular epithelium, and scatered mitotic figures (Fig. 5). The most severe lesions were seen in dogs with the longest survival time, while those dying early had the mildest lesions.

Dogs that survived 10 days had no oxalate crystals in the kidney, and no tubular damage was observed upon euthanasia.

Pulmonary congestion and edema was also a constant finding, but the liver was little, if any, affected. The stomach and intestinal mucosa was markedly hyperemic. The cerebrum and cerebellum contained no significant lesions, and polarized light did not reveal oxalate crystals.

DISCUSSION

Ethylene glycol is readily absorbed from the gastro-intestinal tract and is rapidly and uniformly distributed to the blood and tissues (1). It is oxidized by liver alcohol dehydrogenase to a series of metabolites, with oxalic acid and carbon dioxide as known end products. Oxalic acid combines with calcium to form a calcium oxalate complex which deposits in the renal tubules causing tubular epithelial damage and renal failure. Some EG is excreted unchanged in the urine, but the amount depends upon the species of animal and the dose ingested (2,15). Deaths have usually been attributed to the nephrotoxic actions of the oxalic acid (5,17,23). More recent reports have suggested that toxic intermediates and acidosis are also important factor leading to death (1,18).

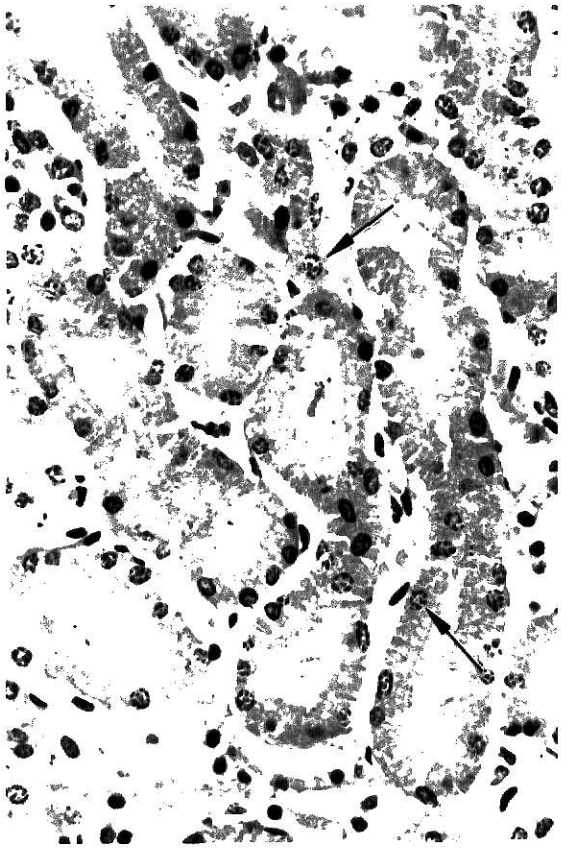

Fig. 5-- Kidney of a dog receiving 8 ml. EG/kg. body weight and treated 4 hours post-dosing. Note karyorrhexis in the tubular epithelium (arrows). H&E stain; x 400.

The effectiveness of the proposed treatment schedule in preventing the toxic action of EG is indicated by the successful recovery of dogs receiving usually lethal doses of this chemical. Within limitations, ethanol was effective in inhibiting the oxidation of EG to the more toxic metabolites, especially glyoxylic acid and oxalic acid. Glyoxylic acid has recently been shown to be the probable toxic factor associated with acute EG deaths (1). The limited oxalic acid production reduced calcium oxalate formation and renal deposition to a non-clinically significant amount (2,18). Administration of the sodium bicarbonate effectively prevented or reversed the occurrence of acidosis, favored increased excretion of the unchanged EG, and reduced calcium oxalate formation (2,3).

Limitations in the proposed treatment were unusually high doses of EG and long periods of time between dosing and the initiation of treatment. With large doses of EG it is possible for even minimal biotransformation of EG to result in sufficient glyoxylic acid production to cause severe toxicity. Furthermore, the administration of large quantities of EG may result in the plasma levels of unchanged EG reaching lethal concentrations (4). Delays in the initiation of treatment allow biotransformation of EG to produce the toxic intermediated and oxalic acid. The development of acidosis is also permitted to proceed unchallanged. The high level of alcohol dehydrogenase activity in

dogs makes this species especially susceptible to time lags in the initiation of appropriate treatment (14).

Since all the control animals and those dogs receiving 10 and 8 ml. EG/kg. body weight and treated 1 and 4 hours respectively post-dosing died acutely, sufficient biotransformation of EG to produce high accumulations of glyoxylic acid probably occurred. This compound has been suggested to interfere with citri-acid intermediates, such as oxalacetate, thus altering this vital biochemical pathway (1). All animals treated early at the 8 and 6 ml. EG dosage level had better survival rates than those treated late. This corresponds with the blocking of EG biotransformation by ethanol and the reduction in glyoxylic acid accumulation.

While all control dogs rapidly developed acidosis, the blood pH in the treated animals was maintained constant by the administration of sodium bicarbonate. Other useful properties of sodium bicarbonate have been suggested as increasing the amount of sodium and citrate excreted in the urine, producing urinary alkalosis, and enchancing the combination of citrate with calcium to reduce the amount of calcium available for combination with oxalic acid (2,3).

The lower BUN values in the treated dogs correspond with inhibition of EG biotransformation and the absence of kidney damage upon recovery. Increasing BUN values related to kidney damage in the treated animals dying from renal failure and uremia. The im-

mediate cause of death in those animals may be attributed to the hyperkalemia and cardiac arrest that follows the uremic syndrome (22,25).

Ethylene glycol produced diuresis in all dogs, but urine specific gravity was within normal ranges for the first 24 hours (19). Thus limited kidney damage occurred indicating only minor nephrotoxic affects due to oxalic acid formation. The uremic syndrome of EG poisoning does not result in death within 48 hours of EG ingestion (18).

While evaluation and statistical interpretation of EG elimination could not be made beyond 24 hours due to death of the control dogs, the high percent of EG recovered in the urine of surviving dogs illustrates the inhibition of EG biotransformation and increased elimination of unchanged EG in the urine by the ethanol-sodium bicarbonate treatment. Availability of frequent small amounts of water helped to maintain fluid balance and kidney function in the treated dogs.

Since the actual amount of EG ingested by spontaneously poisoned dogs in clinical situations is often impossible to determine, these experiments suggest that a clinical reevaluation and prognosis is feasible after 12 to 16 hours of treatment. Animals regaining consciousness between treatments, drinking water, and perhaps walking with difficulty after the third or fourth treatment, can be estimated to have ingested limited amounts of EG. The prog-

nosis for recovery, with completion of the full treatment schedule, is fair to good. Treated animals that will die are usually not able to regain consciousness between treatments.

Renal failure and uremic syndrome is not a common sequel if dogs respond to treatment and if the full 40-hour treatment regimen is systematically applied (27). Development of uremia is clinically evidenced by vomiting, progressively increasing BUN levels, and limited urine production. Prognosis under most clinical circumstances is poor, but peritoneal or hemodialysis and fluid therapy are indicated.

Dogs presented in coma with a history of suspected EG ingestion should be given poor prognosis. These animals are usually in a terminal state of acute intoxication and will not respond to ethanol-bicarbonate therapy. They may also be in the more chronic renal syndrome with terminal uremia.

SUMMARY

A total of 35 dogs were given oral doses of 10, 8 or 6 ml. EG/kg. body weight. EG plasma concentrations, blood pH, blood urea nitrogen, urine total volume, urine specific gravity, urine sediment and urine concentration of EG were measured. Treatment with 5.5 ml. 20% ethanol in physiological saline/kg. body weight IV and 8 ml. 5% sodium bicarbonate in physiological saline/kg. body weight IP was initiated 1, 2, 4, or 6 hours after EG dosing and repeated every 4 to 6 hours for 40 hours.

All 9 control animals died. Seven of seven dogs receiving 10 or 8 ml. EG/kg. body weight died after initial treatment 1 or 4 hours post-dosing. Sixty percent recovery (3/5) was obtained when dogs received 8 ml. EG/kg. body weight and were treated 2 hours post-dosing. Seventy-five percent recovery (3/4) was obtained when dogs received 6 ml. EG/kg. body weight and were treated 4 hours post-dosing. Fifty percent (2/4) was obtained when dogs received 6 ml. EG/kg. body weight and were treated 6 hours post-dosing. Percentage EG recovered in the urine of treated dogs was almost twice as much as that for control dogs.

The proposed treatment effectively inhibited EG biotransformation, as indicated by the high recovery accomplished. Limitations of the treatment included high dosages of EG and long delays in the initiation of treatment. Renal failure and uremia were possible sequela.

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APPENDIX I

LITERATURE REVIEW

History

Ethylene glycol (EG) was synthesized approximately one hundred years ago, and for years it was considered to be non-toxic. To prove this point, one author drank 15 ml. (39) and another 45 ml. (51) without showing signs of toxicity. Due to the shortage of glycerin during World War I, the use of EG as a solvent became widespread (4).

It is not known when the first death from EG poisoning occurred. It has been reported that the first human fatalities occurred in 1930 (49), but it was not until the tragedy of "Massengill's Sulfanilamide Elixer", in which some 76 persons died in 1937, that the toxicity of the glycols was recognized (14).

After this desaster it was shown that diethylene glycol was 72% of the unidentified solvent in the 10% sulfanilamide solution and that it was the primary toxic compound (14). The Massengill's disaster was also a major contributing factor to the modification of United States legislation regarding the labeling and animal testing of new drugs (13).

Since then several hundred cases of serious poisoning caused by EG or related glycols have been published in the human and veterinary literature. It has been estimated that between 40 and 50 people die each year in the United States

from EG poisoning (19,42,51).

Even though animal experimentation began soon after the first human poisoning was described, spontaneous ingestion of EG by dogs was not reported in the United States until 1951, when a 7 year old German Shepherd drank approximately 1 pint of antifreeze and died 24 hours later. The author reported this case as the first such toxicity described in the veterinary literature (23). The first known report of poisoning in cats in the United States was in 1957, when a 6 week old kitten was euthanatized after 2 days of illness and oxalate crystals were found in the renal tubules on postmortem examination (18). Thirty-two clinical cases of EG toxicosis in small animals were reported during 1969 in the United States (38).

Chemistry

Ethylene glycol is also called glycol alcohol, 1-2 ethanol, and glysantin. It is a colorless, odorless, viscous hygroscopic liquid with a bitter-sweet taste, and absorbs twice its weight of water at 100% relative humidity.

It has the structural formula $\begin{matrix} H_2C\text{-}OH \\ | \\ H_2C\text{-}OH \end{matrix}$ and a molecular weight of 62.07. Its specific gravity is 1.113. EG has a boiling point of 197.6°C and a melting point of between -13 and -14°C.

Ethylene glycol is miscible with water, lower aliphatic alcohols, aldehydes and ketones. It is practically insoluble in hydrocarbons and other similar compounds. It is commercially prepared

by the hydratation of ethylene oxide (8,34,43,47).

Uses

Ethylene glycol is used as an antifreeze in cooling and heating systems, principally in motor vehicles. Recently it has also been employed as a circulant coolant in the lunar and other modules developed for the space exploration programs (32). It is further used as an ingredient of electrolytic condensers, as a solvent in the paint and plastic industries, and in the synthesis of safety explosives and certain resinous products (34).

It has been used for pharmaceutical preparations and for external application, but it is banned for internal use in the United States. A topical concentration exceeding 5% is considered a health hazzard (17,43).

Toxicity

The minimum lethal dose for man has long been considered to be 1.6 Gm./kg. body weight (16). However, death has been reported following the ingestion of 60 ml. while other patients have survived 240 ml. (50). Contact with the skin and eyes is most likely to occur in industry, but its low volatility at ordinary temperatures practically eliminates inhalation risk. The minimum allowable concentration of EG in the environment have not been established (8,34,43,47).

The toxicity of EG has been determined in several species

of animals by various authors, but the lethal dose given differs considerably. This variation was explained by Laug (8), to be due to three factors: (1) the number of animals used; (2) the dosage level chosen; and (3) the critical percent mortality selected.

Reports in 1927 (39) showed that dogs given up to 9 ml. EG/kg. body weight by stomach tube showed no untowards effects. Five ml. EG/kg. body weight by the same route induced emesis, and up to 3 ml. EG/kg. body weight injected subcutaneously produced no signs other than slight irritation at the site of injection.

The same author (39) reported that rabbits injected subcutaneously with up to 5 ml. EG/kg. body weight showed no signs of toxicity. When given up to 8 ml./kg. body weight, the rabbits recovered, but when 9 or 10 ml. EG/kg. body weight was administered they died in 12 to 14 hours. Rats injected intraperitoneally with up to 3 ml. of EG/kg. body weight recovered. All rats receiving more than this dose died.

Based upon this results, in 1931, it was stated that EG was "comparatively inocuous as a solvent for medicinals". In the same year and from animal extrapolations the lethal human dose was estimated to be approximately 100 ml. an estimate which was verified by subsequent human fatalities (13,51).

Laug (8) found the oral LD_{50} for rats to be 5.5 ml. EG/kg.

body weight, and for guinea pigs it was 7.35 ml. EG/kg. body weight.

Smyth (8) found the LD_{50} for rats to be 8.54 ml. EG/kg. body weight, and for guinea pigs it was 6.61 ml. EG/kg. body weight. For all animals the route of administration was per os.

Peterson (41) determined the LD_{50} for rats to be 5.8 ml. EG/kg. body weight when given orally and estimated the oral LD_{50} for monkeys to be less than 2.5 ml. EG/kg. body weight. Recently (46) it was stated that the toxic dose of EG for old world monkeys (Maccaca mulatta and M. irus) is probably similar to the 1.6 Gm./kg. body weight established earlier for man.

In dogs, 6.6 ml. EG/kg. body weight was reported to cause death in only 1 of 6 animals. In the same study, 8.8 ml. EG/kg. body weight caused death to 2 of 4 dogs (although the 2 surviving dogs were euthanatized 43 and 46 hours postingestion). Eleven ml. EG/kg. body weight produced death in all 4 dogs used (26) when the compound was administered as a substitute for water to moisten the dry feed. More recent studies have shown death to occur in dogs receiving 4.2 and 4.4 ml. EG/kg. body weight. The oral route of administration was also used (2,24).

In cats, 2 ml. EG/kg. body weight orally was reported as the LD_{50} (15), but 1.5 ml. EG/kg. body weight has also caused death (35).

When given in the drinking water to poultry, 67.5 ml. EG/

liter was reported as the median lethal dose, but clinical signs were observed at a level of 25.0 ml. EG/liter. All birds given 25.0 ml. or more of EG/liter had renal deposition of oxalate salts. Birds on lower levels continuously for two weeks were not affected clinically, but some developed oxalate crystals in the renal tubules (31).

Poisoning has been reported to occur spontaneously in hens in Germany, and later experimental studies demostrated 7.5 ml. EG/kg. body weight to be the lethal dose. The route of administration was not described in this report. In the United States, poisoning has occurred spontaneously in geese (45).

While chronic low-level EG toxicity has not been extensively studied, 1 dog was given 1,036 ml. EG (total dose) in the food over a 6 month period without apparent untoward effects. The estimated dose was 13.2 ml./kg. body weight, but the dog was described as an erratic eater throughout the experiment (27). Chronic studies in monkeys (46) receiving 0.25 to 10% EG in the drinking water resulted in oxalate crystals in the renal tubules when the monkeys received 15 ml./kg. body weight or more. With doses of less than 15 ml./kg. body weight oxalate crystals were not found in the renal tubules, but glomerular damage and azotemia were present. It was suggested that other effects of EG apart of its conversion to oxalic acid were responsible for the pathological changes. Earlier studies (5) had shown that EG

fed at the level of 0.2 and 0.5% of the diet for a period of 3 years produced no toxic effects in monkeys.

Clinical Signs

The clinical signs of EG poisoning have been described for humans as well as for domestic animals (2,8,11,13,17,18,19,23, 24,26,27,29,35,38,43,44,49,51,56). The toxicity usually runs a short course, and there is frequently insufficient time for a through clinical examination as the patient is generally brought to the hospital in a coma. However, the clinical syndrome of EG poisoning has been divided into three stages.

The first stage is that of central nervous system involvement and develops 30 to 60 minutes after ingestion. Nausea, vomiting, signs resembling those of ethanol intoxication, somnolence, occasional diarrhea, ataxia, abnormal placing reflexes, abdominal pain, subnormal temperature, polyuria, hematuria, proteinuria and crystalluria may be seen. Subjective signs in humans have been described as warmth in the throat, mouth and stomach, irritability, and talkativeness. After 4 to 6 hours this stage progresses with severe acidosis to paralysis and coma. Sometimes convulsions develop late in this stage.

An indistinct second stage is that of cardiopulmonary signs. Hyperpnea, tachycardia and moderate tachypnea are consistent early findings, and bradicardia is associated with the terminal stages in fatally poisoned animals. The patient may last 2 to

12 hours while in a coma. Death results from pulmonary edema and/or cardiac failure. Death ussually occurs 8 to 36 hours post-ingestion.

Should the patient survive the first two stages, the third one is that of renal failure due to the precipitation of oxalate salts in the renal tubules. Anuria, uremia, coma and death occur in 5 to 14 days.

Postmortem Lesions

Gross lesions. When a patient dies acutely all the body tissues are congested. There is moderate to marked pulmonary edema and the kidneys are somewhat swollen. Hyperemia of the gastric and intestinal mucosa is also seen. The brain is usually hyperemic, but the degree of severity varies. Generalized edema has been reported in humans (44). The general body condition is a medium to good stage of nutrition (23,26,27,46,50).

If the patient dies in uremia, dehydratation, uremic ulcers in the mouth, and a hemorrhagic gastritis are commonly seen (27,46).

Microscopic findings. The microscopic pathological changes of EG poisoning are so striking as to be almost pathognomonic. Birefringent crystals are found primarily in the proximal renal tubules. These crystals are light-yellow in color and are arranged in different forms and shapes, frequently as sheaves, rhomboid or prisms (13,23,26,27). The crystals are salts of

oxalic acid, principally calcium oxalate, which are formed as end products in the biotransformation process of EG and are deposited in the tubules of the kidneys. They are not readily seen under ordinary light, but appear brillant and double refractile when viewed under polarized light (23,27). The crystals can be identified as calcium oxalate by histochemical techniques. They are stained differentially by the Pizzolato's method. This procedure converts the calcium oxalate to calcium carbonate which stains black with silver nitrate (2,23).

Although occasional oxalate crystals can be found in the kidneys in a variety of diseases, large deposits of them occur only in two known conditions in humans: (1) EG poisoning; and (2) primary oxalosis, a congenital disease of childhood which is believed due to an error in the metabolism of the amino acid glycine (19,29). This latter disease has not been reported in the veterinary literature. Thus oxalate crystals in the kidneys can be considered pathognomonic of EG poisoning in small animals (2,23,26,27).

Hydropic degeneration, dilated tubules, and acidophilic casts are constant findings. The damage to the epithelial cells of the renal tubules increses with the duration of the illness. Swelling and vacuolization of the cytoplasm are seen in animals with the mildest lesions. Hemorrhage and acute inflammatory changes are rarely observed.

The damage to the kidney has been suggested to be of two types (13): (1) a nephrotoxic injury limited to that part of the nephron which is functionally involved in handling the poison, that is the proximal tubule; and (2) an ischemic injury (tubulorrhesis) which occurs variably either diffusely throughout the nephron population, or locally to the individual nephron, as a result of focal cortical ischemia. Since proteinuria occurs at early stages of poisoning, the increased cellularity of the glomerular tuft, the prominence of the epithelial cells, the thickening of the basement membrane, and the granular deposits in the Bowman's space are commonly associated with the proteinuria (13).

Hyperemia and a varied degree of edema are generally observed in the lung. The cause has been attributed to a direct effect of EG, since these changes are usually seen early in the toxicity (13). Bronchopneumonia has also been described in several cases (24,44).

Changes in the central nervous system are slight and difficult to assess. The brain has moderate to marked hyperemia, but there is usually no inflammatory reaction, even though acute encephalitis and meningitis have been reported (44). The cerebellum is also hyperemic and focal loss of Purkinje cells has been observed (13,46). Small birefringent crystals, principally in the blood vessels of the brain have been reported in humans,

dogs, monkeys and rats (13,24,26,27,46,50).

The liver is greatly distended with blood (13,24,26,27,46). Central hydropic degeneration and hepatic fatty change with focal necrosis have been described as common findings in EG poisoning in humans (13,44). Moderate edema and centrolobular hemorrhage have also been described in dogs (27).

Hyperemia of the gastrointestinal mucosa has been cited as a direct toxic effect of EG on the endothelial cells (26).

Cardiac enlargement and myocarditis have been reported in human fatalities (13), but there are no such reports in the veterinary literature.

A few reports have mentioned the toxic effects of EG and/or its metabolites upon the skeletal muscles. Interstitial myositis was reported as earlier as 47 hours postingestion in one patient (13). An interstitial inflammatory reaction in the diaphragm of another patient is also documented (50), but there are no reports of these lesions in small animals.

Physiopathology

The manner in which EG produces its toxicity has not been definitely established (1,7,49,58). EG toxicity has long been related to its biotransformation products. Pohl in 1896 first showed oxalic acid to be the metabolic end product of EG (13). Page in 1926 (39) suggested that due to the structure of EG it would be converted to sugar in the animal body.

For many years oxalic acid was considered the only metabolite responsible for EG toxicity, and there was little doubt that it played a direct role in the nephrotoxicity seen in this poisoning (13,35,49,56).

Ethylene glycol is readily absorbed from the gut of experimental animals and is rapidly and uniformly distributed throughout the blood and tissues (1). However, it was not until the early 1940's that it was determined that rat liver preparations containing alcohol dehydrogenase were able to oxidize EG to oxalic acid (58). Since then, several studies have shown a series of metabolites resulting from the biotransformation of EG (15,16,40,41,54,58).

The complete series of metabolites produced in the biotransformation of EG was developed by Gessner and associates (15,16). Fig. 4 shows them in order of sequence. Gessner showed that the major end product of EG biotransformation was respiratory carbon dioxide and that the main metabolite excreted in the urine was unchanged EG.

In rabbits the end product of the metabolism of (^{14}C2)-EG was respiratory carbon dioxide (60% of the dose in 3 days). In the urine EG was excreted unchanged (10%). Only 0.1% of the administered EG was excreted as oxalic acid. It was suggested that EG is least toxic to species which are able to oxidize it to carbon dioxide and most toxic to species which primarily excrete

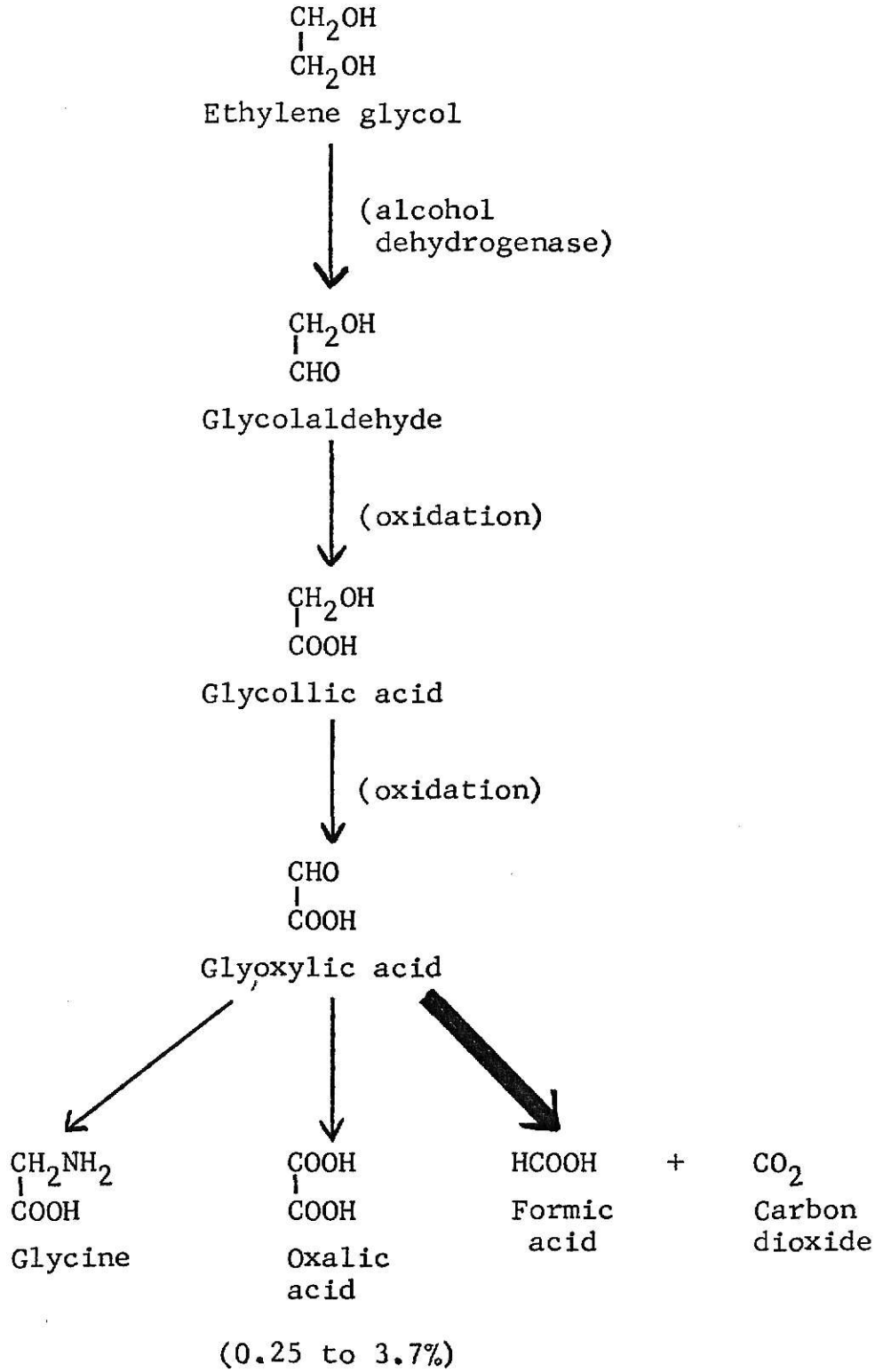

Fig. 4--Biotransformation scheme for EG. Modified after Parke (40).

oxalate salts and the unchanged glycol in the urine.

The amount of EG that is converted to oxalic acid varies with the dose and the species of animals (16,40). For man oxalic acid formation has been established to be less than 2%; for rabbits it is more than 0.37%; in guinea pigs, little or no oxalate is excreted (approximate values are 0 to 0.5%); and in cats 0.7 to 3.7% of the dose is excreted as oxalic acid. The toxicity of EG is higher for cats than for the other species mentioned.

Glucoronic acid conjugation of EG has not been found to occur in man or in experimental animals (15).

Renal tubular oxalosis followed the administration of glycolaldehyde, glycollic acid and glyoxylic acid in rats (7), supporting the sequential degradation scheme of EG proposed by Gessner et al (16). The toxicity of each of the three compounds used was significantly greater than that of the EG itself.

Recent studies in monkeys (Maccaca mulatta) and rats (32) showed that carbon dioxide occurred in the expired air and that unchanged EG appeared in the urine immediately after intravenous administration of small amounts of EG. An oral dose of 1 mg. EG/kg. body weight, which was well tolerated by monkeys, showed peak blood levels in 1 to 2 hours. Twenty-two percent of the dose was excreted unchanged in the urine in 24 hours; no additional excretion occurred in the next 24 hours.

Rats given the same dose of EG by the same route eliminated 32% of the unchanged EG in the urine within 24 hours. After the unchanged EG, the next most important urinary excretion product was glycollic acid. The output of oxalate acid in both species was quite small; approximately 0.3% of the dose for monkeys and 2.5% for rats.

The subcellular effects of EG and some of its major metabolites have been studied using mitochondria isolated from liver, kidney and brain of dogs, rats and monkeys (Maccaca mulatta) (1). Tissue respiration, oxidative phosphorylation and citric-acid activities were unaffected by EG, while substrate-level phosphorylation was inhibited at 10 mM and higher concentrations. In mitochondria from liver, brain and kidney of female rats, respiration was inhibited by 1 mM glyoxylic acid, regardless of the substrate employed. Oxidative phosphorylation was only affected when α-ketoglutarate was the substrate. In parallel experiments with liver mitochondria from male rats, additional uncoupling of oxidative phosphorylation occurred when succinate was the energy source. Mitochondria from dog liver were also susceptible to inhibition by glyoxylic acid. Brain mitochondria from monkeys exposed to concentrations of glyoxylic acid at or above 1 mM had reduced respiration rates, while liver mitochondria from the same species showed only slight reduction in respiration rate and no uncoupling of oxidative phosphorylation when exposed to

glyoxylic acid.

Citric-acid cycle activities were also investigated (1). No effect was shown due to EG except for inhibition of substrate-level phosphorylation at 10 mM and higher concentrations. Glyoxylate inhibited isocitrate and α-ketoglutarate dehydrogenase and substrate-level phosphorylation. It was concluded that at low levels of exposure, adverse effects of EG are most likely attributable to the formation of glyoxylate and the interaction of this metabolite with citri-acid intermediates, such as oxalacetate.

Proposed Treatments

Ethylene glycol poisoning was treated for years as an oxalic acid intoxication (35). Induction of emesis, gastric lavages and calcium therapy were primarily used (8,17,43). However, treatments were almost universally unsuccessful due to the short course of the poisoning and the variable lenght of time between ingestion and initiation of treatment. In the few attempts at treatment reported in the veterinary literature, only supportive measures were used and death occurred in all cases (8,23).

When peritoneal dialysis became available, they became the treatments of choice for EG poisoning. These procedures were used to reduce the blood and tissue levels of EG and its metabolites and also to correct the accompanying severe acidosis. Several reports followed documenting recovery after the ingestion

of lethal doses of EG with several days of oliguria and coma (10,11,13,49,50).

Intensive studies on the biochemical properties of the liver enzyme alcohol dehydrogenase (9,16,22,28,30,31,33,42,54), lead to attempts at a rational competitive antidotal therapy using ethanol, the natural substrate of the enzyme. Peterson et al (41) in 1963 studied the effects of ethanol in experimental EG poisoning. He found that LD_{50} of EG for rats treated simultaneously with ethanol was almost twice of that for untreated rats. In addition, squirrel monkeys (Saimiri sciurea) given toxic doses of EG all died, whereas monkeys receiving ethanol within 30 minutes after the same dose of EG survived. The animals given EG and ethanol excreted an average of 75% of the administered EG unchanged in the urine. The animals given EG alone developed oxaluria and excreted less than 10% of the dose as the unoxidized EG.

Wacker et al (55) successfully used ethanol in 2 men that ingested lethal doses of EG and displayed severe toxic manifestations. The first patient received a total of 3 liters of 5% ethanol during the first 18 hours; the second received an average rate of 11 ml. 95% ethanol/hour for 4 days. Both patients also were treated with sodium bicarbonate to correct acidosis and received repeated peritoneal dialysis. It was suggested that successful therapy must be initiated promptly after EG

ingestion and preferably within 8 hours after ingestion.

Borden (6) tested the value of an alkalinizing agent, such as sodium bicarbonate, in the treatment of EG toxicity. He showed that ethanol and sodium bicarbonate each individually decreased toxicity in rats. However, the highest survival rate and the least tissue toxicity occurred when ethanol and sodium bicarbonate were given together. Sodium bicarbonate was shown to increase the amount of sodium and citrate excreted in the urine. It also produced urinary alkalosis, thus enchancing the combination of citrate with calcium and reducing the amount of calcium available for combination with oxalate (2,6).

In experiments using 10 dogs receiving 4.4 ml. EG/kg. body weight in a dry commercial dog food, 100% recovery was reported when treatment occurred within 30 minutes after ingestion (2). One and one-tenth ml. absolute ethanol and 0.44 Gm. sodium bicarbonate/kg. body weight were given intraperitoneally every 6 hours for 6 treatments. All the 10 control animals died.

Complete recovery was reported in 5 dogs that received 11 ml. EG/kg. body weight orally via a dose syringe (37). Treatment occurred within 1 hour after dosing. A 50% ethanol solution was given intravenously until the dogs were comatosed and could not be aroused by pinching a forelimb digit. The treatment was repeated whenever the dogs responded to that stimulus. The length

of treatment was not mentioned. All 5 control animals died.

Allogenic renal transplant has been used for the treatment of EG poisoning in 1 dog (3). However, the patient died 11 days postsurgery from a generalized mycotic infection.

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APPENDIX II

DOSE: 10 ml. EG/kg. body weight

TREATMENT: Varied

ANIMAL No. 12

Breed: Beagle

Sex: Male

Body weight: 12.3 kg.

Survival time: 38 hours

EG administ.: 123 ml.

% recovered in urine: 40.08

Treatment: At 4 hours after dosing. 20 ml. 5% ethanol in physiological saline/kg. body weight, every 4 hours.

	Blood			Urine		
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	4.0	7.52	7.7	80	1.022	0.015
1	1200.0	-0.01	---	---	---	---
3	1950.0	-0.02	---	---	---	---
6	1500.0	-0.11	---	---	---	---
9	1650.0	-0.10	---	---	---	---
12	1650.0	-0.13	23.2	---	---	---
24	1650.0	-0.17	27.3	1625	1.012	48.09
48	1850.0+	---	---	50	---	49.30

+ Postmortem concentration

ANIMAL No. 13

Breed: Beagle

Sex: Female

Body weight: 14.1 kg.

Survival time: 77 hours

EG administ.: 141 ml.

% recovered in urine: 38.83

Treatment: At 2 hours after dosing. 20 ml. 5% ethanol in physiological saline/kg. body weight, every 4 hours.

		Blood			Urine	
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	1.0	7.51	36.0	75	1.024	0.02
1	1050.0	+0.01	---	---	---	---
3	1650.0	-0.08	---	---	---	---
6	1800.0	-0.09	---	---	---	---
9	1500.0	-0.11	---	---	---	---
12	1500.0	-0.14	74.0	---	---	---
24	1050.0	-0.20	79.5	1833	1.011	51.64
48	6.0	-0.24	178.0	247	1.024	54.64
72	6.0	-0.25	280.0	10	1.026	54.75
77	16.0+	---	---	---	---	---

+ Postmortem concentration

ANIMAL No. 14

Breed: Beagle

Sex: Female

Body weight: 15.1 kg.

Survival time: 31 hours

EG administ.: 151 ml.

% recovered in urine: 27.66

Treatment: At 2 hours after dosing. 10 ml. 20% ethanol in physiological saline/kg. body weight, every 4 hours.

Time after adm.(hour)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	2.5	7.58	6.9	120	1.032	0.02
1	1650.0	-0.03	---	---	---	---
3	1800.0	-0.20	---	---	---	---
6	1800.0	-0.21	---	---	---	---
9	1800.0	-0.23	---	---	---	---
12	1350.0	-0.25	14.0	---	---	---
24	1350.0	-0.47	44.0	1480	1.008	34.49
48	1150.0+	---	---	270	1.006	41.77

+ Postmortem concentration

ANIMAL No. 15

Breed: Beagle

Sex: Male

Body weight: 12.7 kg.

Survival time: 30 hours

EG administ.: 127 ml.

% recovered in urine: 27.66

Treatment: At 2 hours after dosing. 12.5 ml. 10% ethanol in physiological saline/kg. body weight, every 4 hours.

		Blood			Urine	
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	4.5	7.56	5.0	52	1.034	0.013
1	2750.0	-0.01	---	---	---	---
3	2550.0	-0.01	---	---	---	---
6	2250.0	+0.05	---	---	---	---
9	2100.0	+0.08	---	---	---	---
12	1750.0	+0.08	11.5	---	---	---
24	1150.0	-0.02	22.0	1564	1.012	39.62
48	1000.0	---	---	136	1.024	42.98

ANIMAL No. 16

Breed: Beagle

Sex: Female

Body weight: 12.7 kg.

Survival time: 22 hours

EG administ.: 127 ml.

% recovered in urine: 13.36

Treatment: At 1 hour. 50% ethanol in physiological saline until anesthesia was reached and repeated as soon as the animal aroused.

	Blood			Urine		
Time after adm.(hours)	Plasma mg./100ml.	pH ± 0 hours	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	5.0	7.55	8.2	---	---	---
1	2150.0	-0.05	---	---	---	---
3	2550.0	-0.10	---	---	---	---
6	2400.0	-0.35	---	---	---	---
9	2400.0	-0.35	---	---	---	---
12	2400.0	-0.36	36.1	---	---	---
24	1750.0+	---	---	650	1.013	16.97

+ Postmortem concentration

ANIMAL No. 19

Breed: Beagle

Sex: Female

Body weight: 12.8 kg.

Survival time: 37 hours

EG administ.: 128 ml.

% recovered in urine: 26.79

Treatment: At 4 hours. 5.5 ml. 20% ethanol in physiological saline and 8 ml. sodium bicarbonate in physiological saline/kg. body weight, every 6 hours.

		Blood		Urine		
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	0.7	7.58	10.2	---	---	---
1	1450.0	-0.04	---	---	---	---
3	1600.0	-0.04	---	---	---	---
6	1950.0	-0.04	---	---	---	---
9	2400.0	0.0	---	---	---	---
12	1600.0	0.0	9.75	---	---	---
24	1600.0	0.0	22.5	1398	1.015	33.91
48	1450.0	---	---	165+	1.024	37.46

+ Postmortem concentration

DOSE: 10 ml. EG/kg. body weight

TREATMENT: None

ANIMAL No. 11

Breed: Beagle

Sex: Female

Body weight: 12.4 kg.

Survival time: 12 hours

EG administ.: 128 ml.

% recovered in urine: 4.70

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	0.0	7.51	9.5	---	---	---
1	1450.0	-0.03	---	---	---	---
3	1500.0	-0.26	---	---	---	---
6	1750.0	-0.51	---	---	---	---
9	1200.0	-0.75	---	---	---	---
12	1200.0	-0.88	33.4	---	---	---
24	---	---	---	408	1.015	6.023

+ Postmortem concentration

DOSE: 10 ml. EG/kg. body weight

TREATMENT: At 1 hour post-dosing

5.5 ml. 20% ethanol in physiological saline/ kg. body weight.

8.0 ml. 5% sodium bicarbonate in physiological saline/kg. body weight.

ANIMAL No. 17

Breed: Beagle

Sex: Female

Body weight: 11.4 kg.

Survival time: 312 hours

EG administ.: 114 ml.

% recovered in urine: 55.38

Time after adm.(hours)	Plasma mg./100ml.	Blood pH ±0 hour	BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	0.0	7.56	9.45	---	---	---
1	2100.0	-0.05	---	---	---	---
3	2250.0	-0.05	---	---	---	---
6	2100.0	+0.05	---	---	---	---
9	2100.0	+0.04	---	---	---	---
12	1950.0	+0.07	11.5	---	---	---
24	1800.0	0.0	13.5	1353	1.012	45.25
48	13.4	+0.02	14.3	405	1.020	49.74
72	22.5	-0.08	69.0	550	1.018	63.13
96	16.0	-0.11	112.0	---	---	---
168	8.5	-0.14	213.0	---	---	---
240	8.5	-0.13	248.0	---	---	---

ANIMAL No. 39

Breed: Beagle

Sex: Female

Body weight:

Survival time: 15 hours

EG administ.: 127 ml.

% recovered in urine: 27.14

Time after adm.(hours)	Plasma mg./100ml.	Blood pH ±0 hour	BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	0.0	7.54	8.8	620	1.016	0.14
1	850.0	0.0	---	---	---	---
3	1300.0	-0.05	---	---	---	---
6	2100.0	-0.07	---	---	---	---
9	1450.0	-0.04	---	---	---	---
12	1150.0	+0.06	13.4	---	---	---
24	1450.0+	---	---	1505	1.012	34.47

+ Postmortem concentration

ANIMAL No. 40

Breed: Beagle

Sex: Female

Body weight: 11.8 kg.

Survival time: 22 hours

EG administ.: 118 ml.

% recovered in urine: 21.16

		Blood		Urine		
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	2.5	7.56	9.1	210	1.028	0.12
1	1450.0	-0.06	---	---	---	---
3	1750.0	-0.04	---	---	---	---
6	1750.0	0.0	---	---	---	---
9	1750.0	-0.10	---	---	---	---
12	1750.0	0.0	12.3	---	---	---
24	1450.0+	---	37.1	1090	1.013	24.97

+ Postmortem concentration

DOSE: 8 ml. EG/kg. body weight

TREATMENT: None

ANIMAL No. 20

Breed: Beagle

Sex: Female

Body weight: 9.5 kg.

Survival time: 26 hours

EG administ.: 76 ml.

% recovered in urine: 30.79

	Blood			Urine		
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	0.0	7.56	8.5	---	---	---
1	550.0	-0.05	---	---	---	---
3	1600.0	-0.14	---	---	---	---
6	1600.0	-0.28	---	---	---	---
9	1300.0	-0.38	---	---	---	---
12	1150.0	-0.42	21.0	---	---	---
24	1000.0	-0.72	48.6	965	1.013	23.4
48	850.0+	---	---	---	---	---

+ Postmortem concentration

ANIMAL No. 26

Breed: Beagle

Sex: Female

Body weight: 13.6 kg.

Survival time: 9 hours

EG administ.: 108 ml.

% recovered in urine: 8.13

	Blood			Urine		
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	21.0	7.54	11.2	---	---	---
1	700.0	-0.01	---	---	---	---
3	1000.0	-0.20	---	---	---	---
6	1000.0	-0.51	---	---	---	---
9	850.0	---	---	---	---	---
12	---	---	---	---	---	---
24	---	---	---	850	1.015	8.78

ANIMAL No. 27

Breed: Beagle

Sex: Female

Body weight: 10.4 kg.

Survival time: 11 hours

EG administ.: 83 ml.

% recovered in urine: 11.83

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	45.0	7.55	6.7	270	1.022	0.33
1	850.0	-0.02	---	---	---	---
3	1150.0	-0.16	---	---	---	---
6	850.0	-0.39	---	---	---	---
9	700.0	-0.39	---	---	---	---
12	700.0+	---	---	---	---	---
24	---	---	---	950	1.008	9.82

+ Postmortem concentration

ANIMAL No. 36

Breed: Mixed

Sex: Male

Body weight: 6.36 kg.

Survival time: 34 hours

EG administ.: 51 ml.

% recovered in urine: 36.98

	Blood			Urine		
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	5.5	7.56	16.6	---	---	---
1	1750.0	-0.06	---	---	---	---
3	2100.0	-0.15	---	---	---	---
6	2100.0	-0.22	---	---	---	---
9	1750.0	-0.32	---	---	---	---
12	1750.0	-0.37	27.0	---	---	---
24	1300.0	-0.43	74.9	600	1.016	17.78
48	1450.0+	---	---	50	1.018	18.86+

+ Postmortem concentration

DOSE: 8 ml. EG/kg. body weight

TREATMENT: At 2 hours post-dosing

5.5 ml. 20% ethanol in physiological saline/ kg. body weight.

8.0 ml. 5% sodium bicarbonate in physiological saline/kg. body weight.

ANIMAL No. 18

Breed: Beagle

Sex: Female

Body weight: 9.1 kg.

Survival time: Survived

EG administ.: 73 ml.

% recovered in urine: 75.66

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	5.0	7.64	7.5	285	1.020	0.095
1	1600.0	-0.08	---	---	---	---
3	1300.0	-0.12	---	---	---	---
6	1300.0	-0.10	---	---	---	---
9	1300.0	-0.03	---	---	---	---
12	1150.0	-0.03	11.0	---	---	---
24	1150.0	-0.02	17.2	1175	1.012	39.30
48	48.5	-0.04	14.4	595	1.016	54.52
72	21.0	-0.06	13.5	1125	1.010	55.23
96	11.5	-0.02	10.2	---	---	---
168	0.0	-0.06	10.1	---	---	---
240	0.0	-0.04	7.9	---	---	---

ANIMAL No. 24

Breed: Beagle

Sex: Female

Body weight: 9.1 kg.

Survival time: 77 hours

EG administ.: 73 ml.

% recovered in urine: 23.52

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol. ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	0.0	7.52	8.05	110	1.036	0.053
1	850.0	-0.03	---	---	---	---
3	850.0	+0.02	---	---	---	---
6	1150.0	+0.04	---	---	---	---
9	550.0	+0.08	---	---	---	---
12	400.0	-0.02	9.9	---	---	---
24	250.0	+0.10	11.2	1150	1.015	11.88
48	128.0	-0.04	25.5	700	1.016	16.75
72	2.5	-0.07	101.0	600	1.006	17.17
96	0.0+	---	---	---	---	---

+ Postmortem concentration

ANIMAL No. 25

Breed: Beagle

Sex: Male

Body weight: 7.7 kg.

Survival time: Survived

EG administ.: 61 ml.

% recovered in urine: 22.95

Time after adm.(hours)	Plasma mg./100ml.	Blood pH ±0 hour	BUN mg./100ml.	Urine Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	0.00	7.54	6.40	40	1.040	0.02
1	550.00	0.00	---	---	---	---
3	550.00	-0.03	---	---	---	---
6	700.00	+0.11	---	---	---	---
9	550.00	+0.09	---	---	---	---
12	550.00	+0.06	6.40	---	---	---
24	250.00	+0.08	12.10	905	1.020	9.35
48	48.24	0.00	12.80	790	1.024	13.26
72	4.00	0.00	7.15	700	1.012	14.00
96	0.00	-0.20	8.5	---	---	---
168	0.00	-0.05	10.5	---	---	---
240	0.00	+0.04	7.4	---	---	---

ANIMAL No. 32

Breed: Beagle

Sex: Female

Body weight: 8.18 kg.

Survival time: Survived

EG administ.: 65 ml.

% recovered in urine: 83.03

Time after adm.(hours)	Plasma mg./100ml.	Blood pH ±0 hour	BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	EG elim. cum. ml.
0	1.0	7.54	10.1	85	1.030	0.09
1	1750.0	-0.03	---	---	---	---
3	2100.0	-0.04	---	---	---	---
6	1950.0	-0.01	---	---	---	---
9	1950.0	0.00	---	---	---	---
12	1600.0	-0.02	11.4	---	---	---
24	1600.0	+0.02	11.6	830	1.017	20.13
48	31.8	+0.02	11.5	1380	1.012	46.16
72	5.5	+0.02	14.7	870	1.008	53.97
96	4.0	-0.03	12.2	---	---	---
168	2.5	-0.03	11.0	---	---	---
240	2.5	+0.01	9.3	---	---	---

ANIMAL No. 33

Breed: Mixed

Sex: Female

Body weight: 10.45 kg.

Survival time: 336 hours

EG administ.: 83.6 ml.

% recovered in urine: 47.86

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	0.0	7.56	10.1	60	1.028	0.036
1	1750.0	0.00	---	---	---	---
3	2250.0	-0.03	---	---	---	---
6	2250.0	-0.06	---	---	---	---
9	1950.0	-0.02	---	---	---	---
12	1950.0	0.0	11.4	---	---	---
24	1450.0	+0.02	11.6	840	1.019	21.51
48	137.0	-0.01	12.7	600	1.018	36.06
72	11.5	0.00	43.0	800	1.008	40.01
96	7.0	-0.06	83.0	---	---	---
168	5.5	-0.11	103.0	---	---	---
240	2.5	-0.09	130.0	---	---	---

DOSE: 8 ml. EG/kg. body weight

TREATMENT: At 4 hours post-dosing

5.5 ml. 20% ethanol in physiological saline/ kg. body weight.

8.0 ml. 5% sodium bicarbonate in physiological saline/kg. body weight.

ANIMAL No. 21

Breed: Beagle

Sex: Female

Body weight: 7.7 kg.

Survival time: 22 hours

EG administ.: 61.5 ml.

% recovered in urine: 25.61

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	2.5	7.52	8.6	---	---	---
1	400.0	-0.02	---	---	---	---
3	850.0	-0.13	---	---	---	---
6	850.0	-0.08	---	---	---	---
9	700.0	-0.08	---	---	---	---
12	550.0	-0.06	19.8	---	---	---
24	550.0+	---	---	835	1.012	15.75

+ Postmortem concentration

ANIMAL No. 22

Breed: Beagle

Sex: Male

Body weight: 8.63 kg.

Survival time: 28 hours

EG administ.: 69 ml.

% recovered in urine: 44.60

Time after adm.(hours)	Plasma mg./100ml.	Blood pH ±0 hour	BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	0.0	7.52	15.0	67	1.040	0.04
1	700.0	-0.05	---	---	---	---
3	1000.0	-0.05	---	---	---	---
6	1150.0	-0.06	---	---	---	---
9	1000.0	-0.04	---	---	---	---
12	850.0	+0.04	19.7	---	---	---
24	700.0	+0.02	23.6	1110	1.012	29.92
48	850.0+	---	---	95	---	30.77

+ Postmortem concentration

ANIMAL No. 23

Breed: Beagle

Sex: Female

Body weight: 8.63 kg.

Survival time: 23 hours

EG administ.: 69 ml.

% recovered in urine: 14.85

	Blood			Urine		
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	0.0	7.50	9.4	---	---	---
1	1000.0	-0.02	---	---	---	---
3	850.0	-0.14	---	---	---	---
6	700.0	-0.14	---	---	---	---
9	700.0	+0.01	---	---	---	---
12	550.0	+0.02	32.4	---	---	---
24	400.0+	+0.09	91.0	992	1.012	10.25

+ Postmortem concentration

ANIMAL No. 34

Breed: Mixed

Sex: Male

Body weight: 11.3 kg.

Survival time: 36 hours

EG administ.: 90.4 ml.

% recovered in urine: 27.23

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	1.0	7.54	14.9	---	---	---
1	850.0	-0.01	---	---	---	---
3	1150.0	-0.13	---	---	---	---
6	1450.0	-0.09	---	---	---	---
9	1300.0	-0.09	---	---	---	---
12	1150.0	-0.04	17.5	---	---	---
24	1000.0	-0.06	14.9	1220	1.020	24.62
48	1450.0+	---	---	---	---	---

+ Postmortem concentration

DOSE; 6 ml. EG/kg. body weight

TREATMENT: None

ANIMAL No. 28

Breed: Mixed

Sex: Male

Body weight: 10.9 kg.

Survival time: 17 hours

EG administ.: 65.4 ml.

% recovered in urine: 19.04

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	2.5	7.52	12.4	66	1.040	0.060
1	850.0	-0.08	---	---	---	---
3	1750.0	-0.14	---	---	---	---
6	1150.0	-0.22	---	---	---	---
9	550.0	-0.39	---	---	---	---
12	550.0	-0.50	30.5	---	---	---
24	400.0+	---	---	660	1.016	12.45

+ Postmortem concentration

ANIMAL No. 29

Breed: Mixed

Sex: Male

Body weight: 4.6 kg.

Survival time: 19 hours

EG administ.: 27.6 ml.

% recovered in urine: 27.6

Time after adm.(hours)	Plasma mg./100ml.	Blood pH ±0 hour	BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	EG elim. cum. ml.
0	0.0	7.53	16.3	70	1.034	0.038
1	850.0	-0.05	---	---	---	---
3	1450.0	-0.12	---	---	---	---
6	1000.0	-0.26	---	---	---	---
9	1000.0	-0.40	---	---	---	---
12	850.0	-0.47	37.4	---	---	---
24	850.0+	---	---	360	1.014	5.66

+ Postmortem concentration

ANIMAL No. 35

Breed: Mixed

Sex: Male

Body weight: 10.9 kg.

Survival time: 41 hours

EG administ.: 65.4 ml.

% recovered in urine: 35.27

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	2.5	7.52	10.7	60	1.032	0.052
1	1450.0	-0.02	---	---	---	---
3	1750.0	-0.10	---	---	---	---
6	1600.0	-0.11	---	---	---	---
9	1600.0	-0.22	---	---	---	---
12	1150.0	-0.24	19.7	---	---	---
24	1000.0	-0.37	64.0	920	1.014	22.32
48	1600.0+	---	---	40	---	23.07

+ Postmortem concentration

ANIMAL No. 43

Breed: Mixed

Sex: Female

Body weight: 5.45 kg.

Survival time: 35 hours

EG administ.: 32.7 ml.

% recovered in urine: 37.64

	Blood			Urine		
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	8.5	7.56	16.5	---	---	---
1	1600.0	-0.05	---	---	---	---
3	1300.0	-0.11	---	---	---	---
6	1300.0	-0.10	---	---	---	---
9	1150.0	-0.17	---	---	---	---
12	850.0	-0.27	28.1	---	---	---
24	700.0	-0.76	63.0	545	1.012	11.02
48	550.0+	---	86.0	60	---	12.31

+ Postmortem concentration

DOSE: 6 ml. EG/kg. body weight

TREATMENT: At 4 hours post-dosing

5.5 ml. 20% ethanol in physiological saline/ kg. body weight.

8.0 ml. 5% sodium bicarbonate in physiological saline/kg. body weight.

ANIMAL No. 30

Breed: Mixed

Sex: Female

Body weight: 10.9 kg.

Survival time: 264 hours

EG administ.: 65.4 ml.

% recovered in urine: 39.28

Time after adm.(hours)	Plasma mg./100ml.	Blood pH ±0 hour	BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	2.5	7.56	8.1	220	1.040	0.067
1	550.0	-0.04	---	---	---	---
3	1000.0	-0.08	---	---	---	---
6	850.0	-0.04	---	---	---	---
9	850.0	0.0	---	---	---	---
12	550.0	-0.02	9.9	---	---	---
24	400.0	0.0	17.1	930	1.014	14.62
48	61.0	+0.02	17.2	365	1.016	20.36
72	8.5	-0.02	61.0	425	1.024	25.69
96	2.5	-0.06	116.0	---	---	---
168	1.0	-0.07	195.0	---	---	---
240	1.0	-0.06	315.0	---	---	---

ANIMAL No. 31

Breed: Mixed

Sex: Female

Body weight: 10.9 kg.

Survival time: Survived

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	1.0	7.57	8.5	100	1.040	0.122
1	850.0	-0.05	---	---	---	---
3	1150.0	-0.08	---	---	---	---
6	1450.0	-0.03	---	---	---	---
9	1300.0	-0.06	---	---	---	---
12	1150.0	-0.02	10.2	---	---	---
24	850.0	-0.03	14.7	865	1.013	18.65
48	17.5	-0.01	16.9	425	1.022	28.96
72	14.5	-0.01	16.7	365	1.024	31.74
96	5.5	-0.04	19.8	---	---	---
168	4.0	-0.06	23.0	---	---	---
240	1.0	-0.05	19.7	---	---	---

ANIMAL No. 37

Breed: Mixed

Sex: Female

Body weight: 11.8 kg.

Survival time: Survived

EG administ.: 70.8 ml.

% recovered in urine: 77.88

	Blood			Urine		
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	4.0	7.54	7.7	290	1.036	0.035
1	1600.0	-0.04	---	---	---	---
3	2250.0	-0.13	---	---	---	---
6	1750.0	-0.14	---	---	---	---
9	1600.0	-0.06	---	---	---	---
12	1450.0	+0.01	10.1	---	---	---
24	850.0	-0.01	13.4	1530	1.016	45.36
48	57.5	+0.03	8.0	80	1.028	47.73
72	27.0	+0.05	9.4	250	1.036	55.14
96	5.5	+0.01	9.7	---	---	---
168	5.5	-0.02	18.5	---	---	---
240	0.0	-0.01	23.1	---	---	---

ANIMAL No. 38

Breed: Beagle

Sex: Female

Body weight: 9.5 kg

Survival time: Survived

EG administ.: 76.0 ml.

% recovered in urine: 57.87

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	85.0	7.53	9.3	75	1.040	0.102
1	1750.0	-0.02	---	---	---	---
3	2550.0	-0.11	---	----	---	---
6	2550.0	-0.11	---	---	---	---
9	1750.0	-0.11	---	---	---	---
12	1750.0	+0.02	10.1	---	---	---
24	1000.0	+0.05	22.9	1330	1.017	34.05
48	61.0	+0.05	7.0	450	1.022	39.31
72	33.0	+0.05	6.0	520	1.022	43.98
96	11.5	+0.01	11.7	---	---	---
168	5.5	+0.01	19.5	---	---	---
240	5.5	+0.01	9.5	---	---	---

DOSE: 6 ml. EG/kg. body weight

TREATMENT: At 6 hours post-dosing

5.5 ml. 20% ethanol in physiological saline/ kg. body weight.

8.0 ml. 5% sodium bicarbonate in physiological saline/kg. body weight.

ANIMAL No. 41

Breed: Beagle

Sex: Male

Body weight: 10.0 kg.

Survival time: Survived

EG administ.: 60 ml.

% recovered in urine: 46.45

Time after adm.(hours)	Plasma mg./100ml.	Blood pH ±0 hour	BUN mg./100ml.	Urine Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	0.0	7.56	12.8	---	---	---
1	550.0	-0.06	---	---	---	---
3	1000.0	-0.11	---	---	---	---
6	550.0	-0.10	---	---	---	---
9	550.0	-0.08	---	---	---	---
12	400.0	-0.04	10.5	---	---	---
24	400.0	+0.02	11.3	1230	1.020	21.55
48	16.0	+0.01	8.7	435	1.016	27.22
72	5.5	-0.03	8.1	722	1.015	27.87
96	5.5	-0.02	11.9	---	---	---
168	2.5	-0.03	10.1	---	---	---
240	0.0	-0.04	13.8	---	---	---

ANIMAL No. 42

Breed: Beagle

Sex: Female

Body weight: 16.36 kg.

Survival time: 18 hours

EG administ.: 98 ml.

% recovered in urine: 27.43

	Blood			Urine		
Time after adm.(hours)	Plasma mg./100ml.	pH ±0 hour	BUN mg./100ml.	Vol.ml.	Sp.gr.	EG elim. cum. ml.
0	2.5	7.57	7.7	40	1.026	0.024
1	1450.0	-0.03	---	---	---	---
3	1600.0	-0.22	---	---	---	---
6	1600.0	-0.47	---	---	---	---
9	1450.0	-0.26	---	---	---	---
12	1450.0	-0.23	25.9	---	---	---
24	1450.0+	---	---	1280	1.012	26.88

+ Postmortem concentration

ANIMAL No. 44

Breed: Mixed

Sex: Female

Body weight: 10.45 kg.

Survival time: Survived

EG administ.: 62.7 ml.

% recovered in urine: 82.82

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	4.0	7.52	11.4	140	1.036	0.015
1	1150.0	-0.04	---	---	---	---
3	1450.0	-0.10	---	---	---	---
6	1150.0	-0.17	---	---	---	---
9	1150.0	-0.17	---	---	---	---
12	1150.0	-0.08	16.0	---	---	---
24	700.0	-0.01	34.0	1295	1.014	31.13
48	250.0	+0.04	28.8	700	1.016	43.67
72	10.0	+0.04	23.2	800	1.014	51.93
96	7.0	+0.06	17.3	---	---	---
168	2.5	+0.01	16.4	---	---	---
240	2.5	0.00	15.8	---	---	---

ANIMAL No. 45

Breed: Mixed

Sex: Female

Body weight: 10.0 kg.

Survival time: 99 hours

EG administ.: 60 ml.

% recovered in urine: 94.91

Time after adm.(hours)	Blood Plasma mg./100ml.	Blood pH ±0 hour	Blood BUN mg./100ml.	Urine Vol.ml.	Urine Sp.gr.	Urine EG elim. cum. ml.
0	5.5	7.53	14.7	25	1.024	0.015
1	1750.0	-0.02	---	---	---	---
3	2250.0	-0.08	---	---	---	---
6	1600.0	-0.15	---	---	---	---
9	1450.0	-0.11	---	---	---	---
12	1450.0	-0.05	28.8	---	---	---
24	1300.0	+0.01	69.0	1155	1.013	31.13
48	1150.0	-0.01	115.0	480	1.010	41.48
72	57.5	-0.05	169.0	820	1.010	56.95
96	45.5	-0.08	175.0	---	---	---
99	39.5+	---	---	---	---	---

+ Postmortem concentration

A SYSTEMATIC TREATMENT FOR ETHYLENE GLYCOL TOXICITY IN DOGS

by

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D.V.M. University of Guayaquil, Ecuador, 1962

AN ABSTRACT OF A MASTER'S THESIS

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MASTER OF SCIENCE

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Ethylene glycol (EG) toxicity has caused numerous deaths to humans who have ingested it as a cheap substitute for ethanol. Because of its availability it is always a potential hazard for children. It is also a common problem in household pets. The biotransformation of EG has been extensively studied and a series of metabolites has been identified. Definitive identification of the acutely toxic compound has been suggested, but is not yet accomplished.

Antidotal therapy using ethanol, a natural substrate of liver alcohol dehydrogenase the enzyme responsible for EG oxidation, has been used successfully in experimental animals and 2 men. Sodium bicarbonate has been employed to correct acidosis, produce urinary alkalosis, and increase urinary sodium and citrate. The purpose of this study was to devise a clinically effective antidotal treatment schedule for EG poisoning dogs. To this end optimal dosages and concentrations of ethanol and sodium bicarbonate were investigated, and limitations as to dose of EG received and maximal periods of delay in initiation of treatment were studied.

Thirty-five dogs of either sex were used. EG plasma concentrations, blood pH, blood urea nitrogen, urine total volume, urine specific gravity, urine sediment, and urine concentration of EG were measured periodically. Six dogs served to determine the appropriate dosage of ethanol and sodium bicarbonate. An

intravenous dose of 5.5 ml. 20% ethanol in physiological saline/kg. body weight and 8 ml. sodium bicarbonate in physiological saline/kg. body weight intraperitoneally was found most effective. Treatments were repeated every 4 to 6 hours for 40 hours.

Oral doses of 10, 8 and 6 ml. EG/kg. body weight were given to other dog groups. All 9 control animals died. Seven of seven dogs receiving 10 or 8 ml. EG/kg. body weight died after initial treatment 1 or 4 hours post-dosing. Sixty percent recovery (3/5) was obtained when dogs received 8 ml. EG/kg. body weight and were treated 2 hours post-dosing. Seventy-five percent recovery (3/4) was obtained when dogs received 6 ml. EG/kg. body weight and were treated 4 hours post-dosing. Fifty percent recovery (2/4) was obtained when dogs received 6 ml. EG/kg. body weight and were treated 6 hours post-dosing. Percentage EG recovered in the urine of treated dogs was almost twice as much as that for control dogs.

The proposed treatment effectively inhibited EG biotransformation, as indicated by the high recovery accomplished. Limitations of the treatment included high dosages of EG and long delays in the initiation of treatment. Renal failure and uremia were possible sequela, especially if treatment was incomplete.

Guidelines for a favorable clinical prognosis in patients presented with suspected EG poisoning of unknown quantity are:

The regaining of consciousness between treatments, especially between 12 to 16 hours after initiation; the ingestion of water; and the ability to walk even with difficulty after several treatments. Dogs presented in coma should be given poor prognosis because of the probable formation of large amounts of EG intermediates. Those latter animals do not respond to therapy and may be in terminal uremia.