The Effect of Malethamer on the Excretion and Plasma Levels of Sodium, Potassium, and Chloride (34990)

R. H. TUST AND T. M. LIN
(Introduced by R. G. Herrmann)
The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

Malethamer[1] (Fig. 1) the high molecular weight ($>10^6$) copolymer of ethylene-maleic anhydrine cross-linked with vinyl crotonate, inactivates the toxins of *C. botulinum*, *S. aurenus*, *S. typhosa*, and polio virus type 1, and inhibits the growth of a wide variety of bacterial species *in vitro* (1, 2). The incidence of diarrhea in rhesus monkeys induced experimentally by oral administration of magnesium sulfate, castor oil, or Staphylococcus (S_6-strain) enterotoxins is significantly reduced by oral administration of 500–600 mg of malethamer (1, 2).

The copolymer as the anhydride has great affinity for water and forms the dicarboxylic acid upon hydrolysis. The weak acid can then form salts with alkali or bind alkaloids to its reactive sites.

Following the proposal that malethamer be considered for the symptomatic relief of nonspecific acute diarrhea, the effect of the copolymer has been evaluated extensively in patients suffering from diarrhea of various etiological causes. The results of some of these studies have been published (3–5). A question that arises upon repeated or prolonged administration of malethamer is the effect of the copolymer on the electrolyte balance.

Materials and Methods. Rats and dogs were used in this study; the design of the experiment is described in each individual experiment. Sodium (Na) and potassium (K) were determined by flame spectrophtometry utilizing lithium as an internal standard. Cl was determined amperometrically by the method of Cotlove (6).

[1] Malethamer is the generic name of a medical grade of antidiarrheal copolymer of ethylene maleic anhydride and vinyl crotonate supplied to the Lilly Research Laboratories by the Monsanto Company.

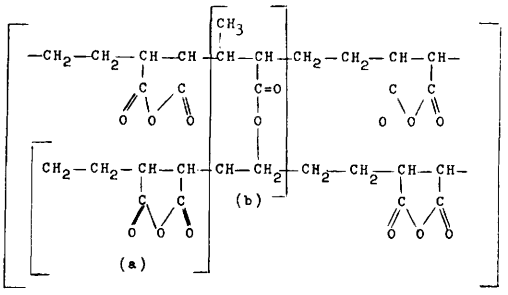

FIG. 1. Ethylene maleic anhydride (a) copolymer cross-linked with vinyl crotonate (b); *n* represents the number of repeating units and is probably >1000.

Results. The effect of malethamer on urinary excretion of electrolytes in the rat. This was studied by a modification of the method of Lipschitz *et al.* (7). Holtzman female rats weighing 160–200 g were fasted overnight and on the day of the test were given orally 15 ml/kg of 0.9% saline containing the test substance suspended in 1% acacia. Control animals received only 1% acacia in saline. Animals were placed in metabolism cages, and the urine was collected for a 4½-hr testing period. For each dose level eight rats, housed two per metabolism cage, were used. At the end of the test period, the urine volume was recorded and the Na, K, and Cl concentrations determined.

The figures shown in Table I represent the means ± SE of the four cages for each dose level and indicate that malethamer at 10–100 mg/kg has no effect on urine flow or renal electrolyte excretion in a 4½-hr test.

The effect of malethamer on total electrolyte excretion in the rat (meq/24-hr). Twenty-four rats were divided into four groups of six animals each. All animals received a control diet of ground Purina Rat Chow for days

TABLE I. Acute Effects of Malethamer on Urinary Excretion of Na, K, and Cl in Rats.[a]

Dose (mg/kg)	Volume (ml)	μeq		
		Na	K	Cl
0	3.6 ± 0.21	372.25 ± 30.6	265.25 ± 30.8	562.75 ± 97.6
10	3.25 ± 0.27	256.25 ± 55.9	210.0 ± 15.06	325.28 ± 41.0
100	3.9 ± 0.55	335.0 ± 48.5	218.4 ± 28.4	479.9 ± 55.4

[a] All the differences are insignificant ($p > .05$); values are mean ± SE for 4½-hr test.

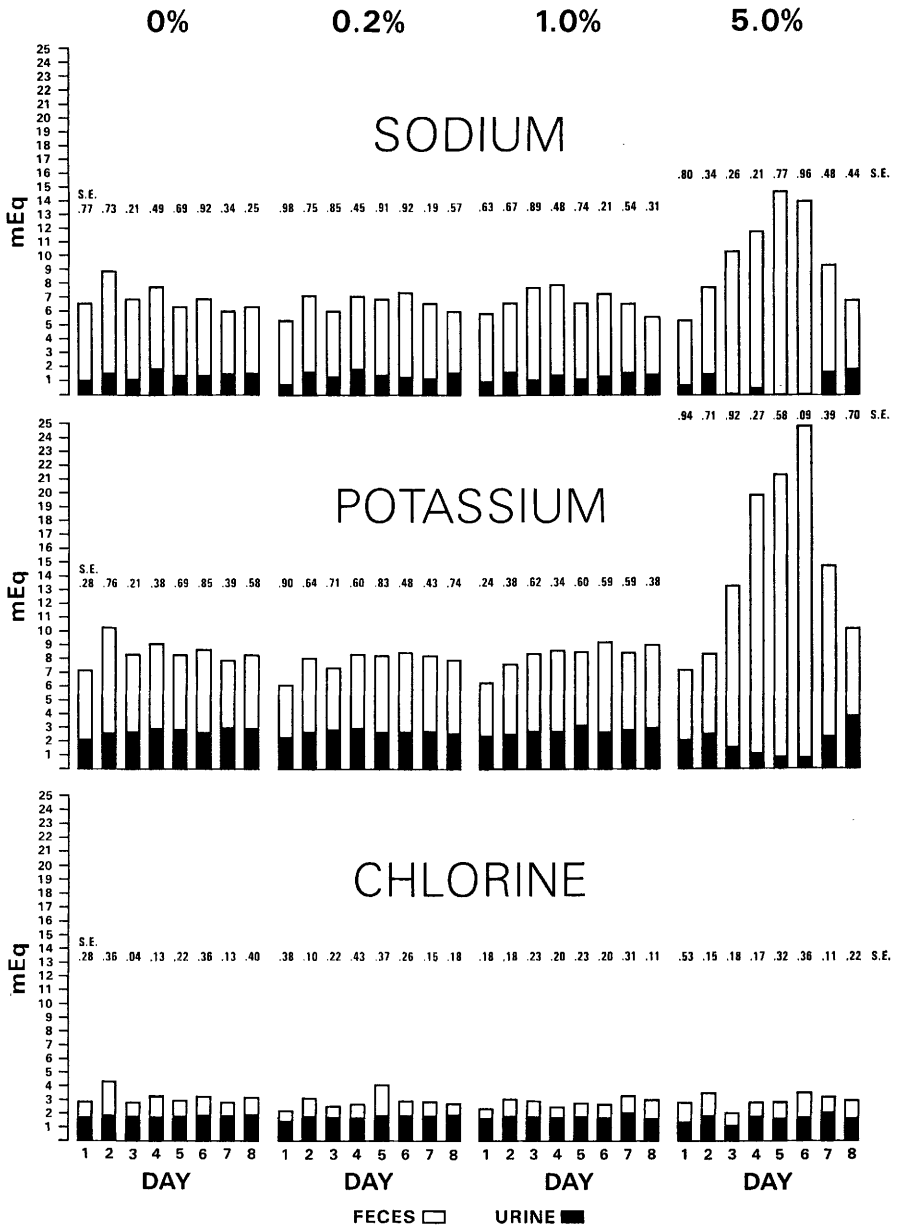

FIG. 2. Total daily fecal and urinary excretion of sodium, potassium, and chloride in rats receiving malethamer at 0–5% levels in the diet.

1 and 2. Immediately after the collection of samples on day 2, diets were changed as follows: Group I, ground Purina Rat Chow; Group II, ground Purina Rat Chow containing 0.2% malethamer; Group III, ground Purina Rat Chow containing 1% malethamer; and Group IV, ground Purina Rat Chow containing 5% malethamer.

After the collection of samples on day 6, all animals were placed on control diets for the next 2 days, the study being terminated on day 8.

Daily urine and fecal samples from each rat were analyzed for Na, K, and Cl. Samples of food were also analyzed for these same components. The fecal and food samples were digested overnight in 0.75 *N* HNO_3 prior to electrolyte determinations.

Data on total fecal and urinary electrolyte excretion are illustrated in Fig. 2, and the average amount of Na, K, and Cl ingested per day is listed in Table II.

The results suggest that the copolymer at 0.2% and 1.0% in the diet had no apparent effect on total electrolyte excretion.

At 5.0% this drug had immediate and marked effects on the excretion of Na and K. Fecal Na and K rose immediately, reaching maximum values on days 5 and 6. In response to this increased fecal loss, urinary Na fell to extremely low levels in the first 24 hr and remained there throughout the duration of drug administration. Urinary K declined gradually but continuously, reaching its lowest point on day 6. Upon cessation of drug administration, fecal Na declined, and urinary Na promptly returned to control levels. Total Na excretion was at control level on the second day after cessation of treatment. Fecal K declined rapidly when the compound was discontinued and was nearly at control level 48 hr later. Urinary K rose to a control level in the first 24 hr with a kaliuresis occurring during the second 24 hr. Total K excretion was approaching the control level 48 hr after the drug was discontinued.

Malethamer had no apparent effect on fecal dry weight, urine volume, or chloride excretion.

Long-term effects of malethamer on plasma Na, K, and Cl levels in dogs. This study was conducted in 8 dogs for 21 months during which 25 (I), 50 (II), 100 (III), and 200 (IV) mg/kg/day of the copolymer was given to two dogs at each dose level. Blood samples were taken intermittently; and the plasma levels of Na, K, and Cl were determined (Table III). The results in Table III indicate that there was a slow but steady decline of Na and K levels in all the animal groups treated. The average plasma Na values stayed within the physiological range (135–160 meq/liter) at the end of the 16-19-month period (8); a very slight drop below this range took place later.

The plasma K levels also stayed within the normal range (3.7–5.8 meq/liter) at the end of 16 months. A slight drop of K below the normal range occurred occasionally in the 16- to 21- month period.

There was no apparent change in the plas-

TABLE II. Average Amounts of Na, K, and Cl Ingested by the Rats per Day (meq).

		Drug conc'n in diet (%)			
		0.0	0.2	1.0	5.0
		Amount ingest.	Amount ingest.	Amount ingest.	Amount ingest.
Day 1	Na	22.1	19.8	21.0	19.6
	K	38.0	33.9	36.0	33.7
	Cl	20.4	18.2	19.4	18.1
Day 2	Na	22.9	21.0	22.4	21.5
	K	39.2	36.0	38.4	36.8
	Cl	21.1	19.4	20.6	19.8
Day 3	Na	23.0	21.3	23.3	17.3
	K	39.4	36.7	39.6	28.9
	Cl	21.2	19.2	21.4	15.7
Day 4	Na	22.8	22.1	22.5	19.4
	K	39.2	38.1	38.2	32.4
	Cl	21.1	19.9	20.6	17.6
Day 5	Na	23.2	22.5	23.7	20.6
	K	39.8	38.7	40.2	34.3
	Cl	21.4	20.2	21.7	18.6
Day 6	Na	21.7	23.2	23.8	22.7
	K	37.2	40.0	40.4	37.8
	Cl	20.0	20.9	21.8	20.6
Day 7	Na	23.2	23.0	23.0	22.7
	K	39.8	39.4	39.4	39.0
	Cl	21.4	21.2	21.2	21.0
Day 8	Na	23.2	22.4	23.2	22.9
	K	39.8	38.5	39.8	39.2
	Cl	21.4	21.1	21.4	21.1

TABLE III. Long-Term Effects of Malethamer on Plasma Na, K, and Cl Levels in Dogs.

Date	Na (meq/liter)				K (meq/liter)				Cl (meq/liter)			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
7–18–61	154	150	153	152	4.5	4.4	4.5	4.4	116	108	108	107
7–21–61	155	154	153	148	4.5	4.8	5.0	4.4	112	111	111	116
8–2–61	144	143	150	141	3.8	4.2	4.2	4.2	112	110	109	111
8–5–61	153	147	156	147	4.2	3.9	4.5	4.2	118	113	109	117
10–31–61	147	146	147	148	4.7	4.3	4.7	4.2	107	108	107	107
12–4–61	147	145	144	142	4.6	4.8	5.1	4.6	110	111	108	117
2–5–62	133	132	133	147	3.7	4.1	3.7	4.1	113	116	114	108
4–6–62	136	136	143	148	4.2	4.2	4.5	4.3	111	106	109	106
5–9–62	141	144	149	139	4.5	4.6	4.8	4.2	113	111	111	112
7–10–62	136	142	133	144	3.4	4.6	3.4	3.7	117	108	108	107
8–13–62	130	129	129	129	4.2	3.8	4.4	4.0	117	107	112	116
9–10–62	136	137	137	137	4.2	4.1	4.2	4.2	112	113	115	115
10–15–62	137	137	139	136	4.0	3.9	3.9	4.0	115	118	119	115
12–10–62	136	138	136	137	3.6	3.8	3.6	3.8	114	115	114	110
1–17–63	135	134	139	144	3.8	3.9	4.2	4.1	117	116	121	111
2–14–63	133	136	133	132	3.1	3.3	3.4	3.6	121	115	129	120
3–15–63	131	140	136	135	3.9	3.9	4.0	4.3	119	118	119	120
4–12–63	129	134	128	128	3.7	3.8	3.6	3.4	117	115	120	116

ma chloride content for all dietary groups over a period of 12 months. However, during the 13- to 21-month period a slight rise (1–11 meq/liter) of Cl took place in groups II, III, and IV.

Discussion. The results indicate that in acute experiments malethamer had no effect on the urinary excretion of electrolytes at 100 mg/kg. In subacute studies fecal Na and K excretion was significantly increased while urinary Na and K outputs were reduced by malethamer at 5% in the diet. In chronic studies in the dog, plasma K and Na levels remained within normal ranges for as long as 16 months on the diet after which only a slight drop below normal values took place at all dose levels. The chloride contents were not affected in any of these tests indicating that only the cations were bound by malethamer.

Diet consumption by these young rats weighing 160–200 g was about 20–22 g/day. In a diet containing 5% of malethamer, the amount of malethamer ingested was 1.0–1.1 g/kg/day. The effective doses for the prevention of experimental diarrhea induced by either Staphylococcus enterotoxin, or $MGSO_4$, or castor oil was 200–300 mg/kg in the monkey (1). Those for preventing diarrhea in the infants (4) and in man (3) were 120–300 and 50 mg/kg/day, respectively. All these therapeutic doses were lower than that used in the rat. Long-term feeding of malethamer to dogs for more than a year at doses of 25–200 mg/kg/day may reduce the Na and K levels in the plasma below the normal ranges; the results in Table III indicate a lowering of Na and K by approximately 1–4 and 0.3–0.6 meq/liter, respectively. This is consistent with the property of malethamer which binds cations. The chloride content in the plasma remained unchanged in 16 months after which a slight increase took place in dogs receiving 50–200 mg/kg/day.

Summary. The effect of malethamer on the excretion of electrolytes was studied in the rat. A single dose of 100 mg/kg p.o. had no effect on urine output of Na, K, and Cl. A diet containing 5% malethamer increased fecal but decreased urinary excretion of Na and K. The plasma Na and K levels of dogs on diets containing 25–200 mg/kg/day remained within normal ranges over a period of 16 months after which only some slight drops took place. The plasma Cl level was not affected by malethamer.

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