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The Toxicity and Laxative Action of Sodium Fumarate*

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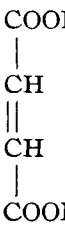
The salts of several carboxylic acids, such as tartaric, citric and gluconic acid, are known to possess laxative properties, and some of them are strongly nephropathic. The present report is concerned with a study of the toxicity and the laxative properties of sodium fumarate.

Fumaric acid is a dicarboxylic acid with the formula:



It was used in the form of the disodium fumarate.

EXPERIMENTAL

ANIMAL EXPERIMENTS

Rabbits and cats were used in these experiments. Several types of observations were made to study toxicity. The behavior, the appearance and the weight of the animals were recorded. Blood examinations were made for evidence of non-protein nitrogen (N. P. N.) (1) and creatinine (2) retention. The jugular vein was exposed through a small incision of the skin. This greatly facilitated the collection of blood samples. The wound showed little tendency to infection. Phenolsulfonephthalein (P. S. P.) excretion tests were made (3). The urine was examined for albumin, casts, reducing substances and red blood cells. These observations were made prior to, and for varying numbers of days after, the administration of the drug. The final data included approximately 90 of each of the foregoing examinations.

At autopsy, the organs were inspected grossly, and in the case of the liver and kidney, microscopic sections were also examined (in all, 44 sections). In animals that were sacrificed, the tissues were fixed immediately in 15 per cent formalin solution. Paraffin sections were made and stained with hemotoxylin and eosin. Postmortem changes complicated the histological examination on those cases in which the animal died during the night.

All doses were given by intravenous injection in 10 or 15 per cent solution in water. This route of administration provided the more severe test of the systemic toxicity of the drug.

Single Dose in Rabbits.—The effect of a single intravenous injection of disodium fumarate was studied in one group of 9 rabbits. The essential data are summarized in Table I. The doses varied from 0.05 to 2.0 Gm. per Kg. of body weight. Anticipating that severe poisoning by the fumarate might result in anorexia, we first planned this group of experiments in fasting animals.

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Table 1.—The Effect of a Single Intravenous Dose of Sodium Fumarate, Sodium Tartrate and Sodium Chloride

Animal No. Initial and final weight (Kg.)	Dose, Gm./Kg.	N. P. N.	Creatinine	P. S. P.	Liver	Histology Kidneys	Remarks
			Rabbits (Fumarate)				
1	0	52 (0)[a]	2.1 (0)	80 (0)	Normal	Cloudy swelling in tubules[b]	Died after fasting 9 days
I. W. 2.51		...	...	65 (1)			
F. W. 1.84		48 (2)	...	100 (2)			
		59 (4)	2.1 (4)	90 (4)			
		60 (6)	1.8 (6)	88 (6)			
		83 (8)	2.1 (8)	68 (8)			
2	0	...	...	100 (0)	Post-mortem degeneration	Post-mortem degeneration[b]	Died after fasting 11 days
I. W. 2.26		72 (2)	2.4 (2)	95 (2)			
F. W. 1.34		91 (3)	2.4 (3)	...			
		74 (4)	2.5 (4)	71 (4)			
		90 (6)	2.5 (6)	75 (6)			
3	0.05	53 (−2)	1.5 (−2)	45 (−2)	...	...	See Table II
I. W. 2.62		55 (−1)	1.1 (−1)	72 (−1)			
F. W. 1.83		...	...	85 (0)			
		59 (+2)	1.4 (+2)	90 (+2)			
		58 (+4)	1.5 (+4)	88 (+4)			
		55 (+6)	1.4 (+5)	74 (+6)			
4	0.20	48 (−2)	1.8 (−2)	90 (−2)	...	...	See Table II
I. W. 2.50		48 (−1)	1.8 (−1)	70 (−1)			
F. W. 1.8		...	...	80 (0)			
		50 (+2)	2.4 (+2)	90 (+2)			
		46 (+4)	2.4 (+4)	78 (+4)			
		51 (+6)	2.4 (+6)	91 (+6)			
5[c]	0.50	37 (0)	1.6 (0)	98 (0)	Normal	Slight cloudy swelling; weight, 10 Gm.[b]	Died 3 days after dose
I. W. 2.83		35 (+1)	1.6 (+1)	84 (+1)			
F. W. 2.80							
6[c]	0.50	...	...	...	...	...	Died of pulmonary edema 10 min. after rapid injection
I. W. 3.17							
7	0.60	52 (−2)	2.2 (−2)	50 (−2)	Normal	Normal[b]	Was found depressed and week 2 days after dose. Died 1 hr. 18 min. after last blood sample, and after fasting 5 days
I. W. 2.70		52 (−1)	2.7 (−1)	45 (−1)			
F. W. 1.97		...	...	50 (0)			
		168 (+2)	5.0 (+2)	...			
8	0.60	54 (−1)	1.7 (−1)	95 (−1)	Normal	Tubules show marked granular swelling[b]	Died after fasting 6 days
I. W. 2.32		62 (0)	1.7 (0)	100 (0)			
F. W. 1.87		61 (+1)	1.7 (+1)	90 (+1)			
		102 (+3)	1.8 (+3)	90 (+3)			
9	1.00	55 (−1)	2.0 (−1)	95 (−1)	Normal	Tubules show marked granular swelling	Died after fasting 7 days; in clonic convulsions for 20 min.
I. W. 2.12		54 (0)	1.9 (0)	100 (0)			
F. W. 1.82		53 (+1)	1.7 (+1)	93 (+1)			
		72 (+3)	2.5 (+3)	92 (+3)			
10[c]	1.00	46 (0)	1.7 (0)	87 (0)	Normal	Normal; weight, 17 Gm.	Died of clonic convulsions 11 days after dose. Brain section also normal
I. W. 2.26		53 (+1)	1.5 (+1)	93 (+1)			
F. W. 2.28		52 (+3)	1.6 (+3)	79 (+3)			
		36 (+5)	1.4 (+5)	64 (+5)			
		44 (+8)	1.2 (+8)	91 (+8)			
		41 (+10)	1.0 (+10)	99 (+10)			
11[c]	2.00	...	...	...	...	...	Died of pulmonary edema 10 min. after injection
I. W. 2.96							
			Rabbits (Tartrate)[d]				
12[c]	0.20	46 (0)	1.3 (0)	110 (0)	Post-mortem degeneration	Granular swelling of tubules. Weight, 27 Gm.[b]	Died 5 days after injection
I. W. 3.14		81 (+1)	2.4 (+1)	58 (+1)			
F. W. 2.70		69 (+2)	2.0 (+2)	53 (+2)			
13[c]	0.30	49 (0)	1.6 (0)	93 (0)	Normal	Normal; weight 25 Gm.	Died 8 hrs. after injection, in convulsions. No gross pathological findings
I. W. 2.78							
F. W. 2.78							

Animal No. Initial and final weight (Kg.)	Dose, Gm./ Kg.	N. P. N.	Creatinine	P. S. P.	Liver	Histology Kidneys	Remarks
14	0.30	44 (−1)	2.0 (−1)	75 (−1)	Normal	Different from fumarates. Marked tubular swelling with Ca deposits. Nephrosis. Weight, 38 Gm.[b]	Died after fasting 7 days
I. W. 2.96		45 (0)	2.1 (0)	91 (0)			
F. W. 2.78		88 (+1)	6.8 (+1)	1 (+1)			
			Rabbit (Sodium Chloride)				
15	0.20	43 (1)	1.8 (1)	100 (1)	...	Weight, 14.5 Gm.	Died on 2nd day, in clonic convulsions for 3 min.
I. W. 2.45							
F. W. 2.45							
1[c]			*Cats (Fumarate)*				
I. W. 2.73	0.00	49 (0)	2.2 (0)	40 (0)	...	...	Used for tartrate injection, and designated cat 1A (see below)
F. W. 2.98		70 (1)	2.0 (1)	69 (1)			
		42 (3)	1.7 (3)	54 (3)			
		44 (5)	1.7 (5)	50 (5)			
		34 (8)	1.7 (8)	51 (8)			
		44 (10)	1.5 (10)	66 (10)			
2[c]	1.00	51 (0)	1.8 (0)	66 (0)	Normal	Normal; weight, 22 Gm.	Immediately after injection, respiration became rapid and animal depressed. Sacrificed 25 days after injection
I. W. 3.00		48 (+1)	1.5 (+1)	91 (+1)			
F. W. 3.15		32 (+3)	1.4 (+3)	73 (+3)			
		25 (+5)	1.2 (+5)	61 (+5)			
		30 (+8)	1.4 (+8)	75 (+8)			
		36 (+10)	1.3 (+10)	76 (+10)			
		47 (+25)	1.3 (+25)	65 (+25)			
			Cat (Tartrate)[d]				
1A[c]	0.30	44 (0)	1.5 (0)	66 (0)	Fatty infiltration	Large scar (about 2 cm. long) in both kidneys noted grossly although section examined was normal. Weight, 25.5 Gm.	2+ albumen and 4+ glucose in urine 4 days after injection. 4+ glucose 7 days after injection. Urine normal thereafter. Animal sacrificed 15 days after injection
I. W. 2.98		107 (+1)	5.7 (+1)	0 (+1)			
F. W. 3.10		98 (+4)	3.1 (+4)	23 (+4)			
		64 (+7)	2.1 (+7)	47 (+7)			
		68 (+15)	1.7 (+15)	60 (+15)			

[a] Numbers in parenthesis indicate days in relation to the injection; thus (−2) represents 2 days before injection, (0) on day of injection, (+2) 2 days after injection.
[b] These animals died during the night.
[c] These animals were fed; all others were fasted except for unrestricted water.
[d] The dose is stated as tartaric acid.

Two additional rabbits were studied as controls without drug, as a check against the effect of fasting, as well as of other conditions in the laboratory which might prove unfavorable to the health or renal function of the experimental animals. We soon learned that the slow intravenous injection of fumarate in the doses given was usually without immediate effect on the appearance or the behavior of the rabbits, nor did it produce anorexia. Subsequent experiments were made with rabbits fed 4 ounces of rabbit pellet food and 3 to 4 cabbage leaves daily.

It may be noted that 7 of the 9 rabbits which received a single intravenous dose of the fumarate died. In two cases death resulted from pulmonary edema within 5 and 10 minutes, respectively. In one of these the dose was very large (2 Gm. per Kg. in 15 per cent solution); in the other, 0.5 Gm. in 15 per cent solution per Kg. was injected very rapidly. These effects are probably non-specific and may be due to the sudden change in tonicity of the blood or to direct pulmonary capillary irritation. Of the 5 fasting rabbits in which the injections were made slowly, 2 showed no effects and survived (doses 0.05 and 0.20 Gm. per Kg.) and 3 died after total fasting periods of 5, 6 and 7 days, respectively (doses 0.6, 0.6 and 1.0 Gm. per Kg.). Fasting may have played an important part in these deaths, since the two control rabbits died after fasting 9 and 11 days, respectively. Inasmuch as rabbits Nos. 5 and 10, which were fed throughout and lost practically no weight from the beginning to the end of the experiments, also died in 3 and 11 days, respectively, after the dose, it seems safe to assume that an intravenous injection of disodium fumarate in a dose of 0.5 Gm. or larger is toxic to rabbits and may prove fatal. In those cases in which the mode of death was seen, it frequently involved myoclonic convulsions. At autopsy there were no gross pathological changes to account for the fatal outcome. The mechanism of this form of poisoning remains unexplained. It may also be a non-specific action, since we observed death with clonic convulsions after the intravenous injection of sodium tartrate and of sodium chloride.

Table I shows that after the fumarate there occurred changes in the blood chemistry which might

suggest some renal injury, but the renal effects are, on the whole, equivocal in this group of experiments. Two animals, rabbits 5 and 10, which were fed, showed no significant changes (doses 0.5 and 1.0 Gm. per Kg.). In 2 (rabbits 7 and 8) of the 5 fasting animals there was marked elevation of the N. P. N. The significance of this is problematical, since the 2 control fasting animals (rabbits 1 and 2) also showed a rising N. P. N. and it has been shown by others (4) that fasting itself causes a rise of the blood N. P. N. In rabbit No. 7 with the highest N. P. N. (168 mg.), the blood sample was taken when the animal was nearly moribund, 1 hour and 18 minutes before death.

The histological examination of the kidneys in the case of the animals receiving fumarates showed tubular changes in some cases. These were, however, similar to the changes found in the control fasting rabbit, but in 2 cases (rabbits 8 and 9) they were more marked.

In view of the well-known nephropathic action of the tartrates, the effect of sodium tartrate was studied in 3 rabbits for comparison. A dose of 0.3 Gm. per Kg. caused death with convulsions within 8 hours and no histological changes in the kidneys. A similar dose of 0.3 Gm. to another rabbit caused, within 24 hours, severe tubular degeneration with profound functional changes, as shown by a rise of N. P. N. by about 100 per cent, of the creatinine to about 300 per cent, and a fall of the P. S. P. to 1 per cent. A smaller dose of 0.2 Gm. produced similar but less marked effects. The marked increase in the weight of the kidneys also distinguishes the effects of tartrate from those of the fumarate. The contrast of the histological changes in the kidneys of the tartrate and fumarate animals was very striking.

It is clear from the foregoing experiments that when tested by the single intravenous injection, the nephropathic action of disodium fumarate in rabbits is slight by comparison with tartrate. Whereas a dose of 0.3 Gm. of the tartrate caused severe nephrosis, the effect on the kidney of a dose of 1.0 Gm. of the fumarate was negligible.

Single Dose in Cats.—The above experiments were repeated in cats. The results were essentially similar to those obtained in rabbits. A dose of 0.3 Gm. of

Table II.—The Effect of Repeated Intravenous Doses of Sodium Fumarate and Sodium Chloride

Rabbit No. Initial and final weight (Kg.)	Dose Gm./Kg.	Total No.	Period in Days during Which Drug Was Given	N. P. N.	Creatinine	P. S. P.	Histology Liver	Histology Kidneys	Remarks
16	0.30	7	1–16	43 (1)[a]	1.6 (1)	104 (1)	Marked	Normal;	Sacrificed on 16th day
I. W. 3.11	NaCl			50 (9)	1.5 (9)	82 (9)	cloudy	weight,	
F. W. 2.73				76 (15)	1.8 (15)	...	swelling	14.5 Gm.	
				..	...	90 (16)			
17	0.50	7	1–16	51 (1)	1.9 (1)	105 (1)	Some	Normal;	Sacrificed on 16th day
I. W. 2.77	NaCl			45 (9)	1.5 (9)	92 (9)	cloudy	weight,	
F. W. 3.05				46 (15)	1.8 (15)	...	swelling	13 Gm.	
				..	...	75 (16)			
18	0.20	6	1–11	36 (1)	1.5 (1)	109 (1)	Slight	Normal;	Sacrificed on 16th day
I. W. 2.60	0.50	3	12–16	45 (9)	1.6 (9)	77 (9)	cloudy	weight,	
F. W. 2.47				49 (15)	1.7 (15)	...	swelling	16.5 Gm.	
				..	...	68 (16)			
19	0.30	7	1–16	54 (1)	1.7 (1)	72 (1)	Slight	Normal;	Sacrificed on 16th day
I. W. 2.74				52 (9)	1.0 (9)	78 (9)	cloudy	weight,	
F. W. 3.09				48 (15)	1.4 (15)	...	swelling	16.5 Gm.	
				..	...	87 (16)			
20	0.50	6	1–13	57 (1)	1.6 (1)	97 (1)	Normal	Normal;	Sacrificed on 13th day. Severe infection of soft tissues at site of dye injection for 4 days prior to last blood and P. S. P. tests
I. W. 2.31				38 (9)	1.3 (9)	78 (9)		weight,	
F. W. 2.40				37 (13)	1.1 (13)	19 (13)		14.5 Gm.	
3	0.05	5	1–10	38 (3)	1.5 (3)	92 (3)	Normal	Cloudy	Died 20 hrs. after last dose in clonic convulsions
I. W. 1.83				50 (10)	1.4 (10)	...		swelling;	
F. W. 1.74								tubular degeneration	
4	0.20	13	1–32	33 (3)	1.9 (3)	74 (3)	Fairly	Slight	Sacrificed on 32nd day
I. W. 1.86				27 (5)	1.7 (5)	...	marked	cloudy	
F. W. 2.50				..	...	84 (8)	cloudy	swelling;	
				38 (10)	1.4 (10)	67 (10)	swelling	weight,	
				45 (17)	1.5 (17)	79 (17)		14.5 Gm.	
				65 (25)	2.1 (25)	81 (25)			
				59 (31)	2.1 (31)	...			
				..	...	94 (32)			

[a] Figure in parenthesis represents the day during the period of injection when the test was made.

tartrate per Kg. in one cat caused marked nephropathy with considerable elevation of the blood N. P. N. and creatinine, and a decline of the P. S. P. excretion from 66 per cent to zero. In addition, albuminuria and glycosuria resulted. At autopsy, large scars were found in the kidneys, although in the intervening 15 days the results of chemical tests of the blood and urine had returned to normal. In contrast to these changes, a dose of 1 Gm. of fumarate per Kg. in another cat produced neither chemical nor anatomical changes in the course of 25 days.

Repeated Doses in Rabbits.—Each of 5 rabbits received a series of intravenous injections of sodium fumarate at intervals of 2 to 3 days for periods of from 10 to 32 days. These animals were fed throughout the experiments. The total number of injections ranged from 5 to 13. The single doses ranged from 0.05 (rabbit 3) to 0.5 (rabbit 20) Gm. per Kg.; the total doses received by the different rabbits, from 0.25 to 3.0 Gm. per Kg. The results are summarized in Table II. One of the animals (rabbit 3) died in clonic convulsions on the tenth day after a total dose of 0.25 Gm. per Kg. All the others were well throughout the experiments and survived, although they had received much larger total doses. There were no significant changes in the blood chemistry, urine or P. S. P. excretion in any of the animals. The low P. S. P. excretion, 19 per cent, on the thirteenth day in rabbit 20, was probably due to impaired absorption of the dye as a result of infection at the site of injection. In rabbit 4, the N. P. N. rose from 33 to 65 mg. Whether this was a specific effect of the fumarate is a matter of doubt, since a similar rise was obtained in rabbit 16 which received repeated injections of sodium chloride. The kidneys showed no histological changes, with the exception of those of rabbits 3 and 4 in which there was some cloudy swelling. These animals were carried over from the previous series of experiments in which they had been fasted, and, as has already been indicated, the fasting control also showed cloudy swelling. The experiments with repeated injections of fumarate in non-fasting animals, therefore, give no evidence of nephropathic action.

OBSERVATIONS IN MAN

The laxative action and the toxic effects of sodium fumarate were studied in a group of 26 patients. There were all confined to bed in the hospital for a wide variety of medical and surgical disorders. The description of this group of cases is summarized in Table III. They all suffered with either acute or chronic constipation. Both sexes and a wide range of ages, from 11 to 67 years, are represented. Many of these patients were accustomed to the use of enemas or laxatives, such as milk of magnesia, Ex-lax, cascara, mineral oil, etc., which were taken habitually at intervals ranging from 1 day to 2 weeks.

When they were in need of a laxative, a dose of fumarate was administered. The dose was given after the patients had been without a bowel movement for periods ranging from 21 to 114 hours—in the majority of cases, for a period of 48 hours or longer. The dose was dissolved in half a glass of water and administered orally at bedtime. Each of 10 patients received one dose. In the remaining 16, the recurrence of constipation afforded the opportunity of using the fumarate from 2 to 6 times. The doses ranged from 5 to 30 Gm. The 26 patients received a total of 65 doses. If the bowels did

Table III.—Description of 26 Patients Used in Present Study

Case No.		Age	Sex	Acute or Chronic	Duration of Constipation	Intervals Between Doses in Habitual Use of Laxatives (Days)	Remarks
1	A. D.	31	F	Chronic	5 yrs.	1–2	.....
2	A. E.	19	M	Acute	3 mo.	7	Only when confined to bed
3	M. A.	62	F	Chronic	Many yrs.	10–14	Especially since confined to bed
4	R. B.	50	F	Acute	25 yrs.	...	Only when confined to bed
5	G. B.	25	F	Chronic	5 yrs.	1	.....
6	S. A.	56	F	Acute	1 wk.	...	Only when confined to bed
7	M. C.	71	M	Chronic	Many yrs.	7	.....
8	R. S.	47	F	Acute	1 wk.	...	Only when confined to bed
9	H. D.	48	F	Chronic	Several yrs.	14	.....
10	S. M.	11	F	Acute	1 wk.	...	Only when confined to bed
11	R. L.	59	F	Chronic	Many yrs.	1–2	.....
12	J. P.	67	M	Chronic	25 yrs.	2–3	.....
13	S. F.	59	F	Chronic	Many yrs.	2–4	.....
14	R. O.	46	F	Chronic	Many yrs.	1	.....
15	A. P.	20	M	Acute	4 wks.	4–7	Only when confined to bed
16	J. S.	60	M	Chronic	5 yrs.	2	.....
17	M. B.	18	F	Chronic	Many yrs.	3	.....
18	G. Ba.	28	F	Acute	1 wk.	...	Only when confined to bed
19	R. Br.	14	F	Acute	1 wk.	...	Post-operative
20	E. A.	43	F	Chronic	10 yrs.	2	.....
21	A. R.	22	F	Chronic	8 yrs.	1	.....
22	P. S.	21	F	Acute	2 mo.	3–4	Only when confined to bed
23	A. S.	47	F	Acute	3 days	...	Only when confined to bed
24	E. S.	31	F	Acute	5 wks.	3	Occasional laxative at home
25	B. F.	31	F	Acute	6 wks.	2–3	Only when in bed and when on iron therapy
26	T. S.	24	F	Acute	2 days	...	.....

not move within 24 hours, the dose was considered ineffective.

With the doses used in this study, a bowel movement was produced by 38 or 59 per cent of the 65 doses, and in 18 of the 26 patients. As is the case with all laxatives, the sensitiveness of different individuals to the laxative action varied considerably, some responding to a dose of 5 Gm., while in others a dose of 30 Gm. proved ineffectual. The response to the action of the fumarate varied in the same individual at different times. For example, in case 24, at one time, a dose of 10 Gm. produced a laxative effect in 18 hours; subsequent doses of 20 and 15 Gm. produced no effect, while at still another time a 25-Gm. dose produced a laxative effect in 2 hours.

The laxative effect occurred in an average of 10 hours after the dose, the range being from 1 to 22 hours. With respect to the relation between the speed of the laxative effect and the size of the dose, the results showed that the rapid effects (from 1 to 6 hours after the dose) are fairly evenly distributed between the larger and the smaller doses. Also, the incidence of laxative effects bore no relation to the size of the dose in the range of doses which were used. For example, the 7 doses of 5 Gm. each produced laxative effects in 5 instances, and the 7 doses of 25 Gm. each similarly produced laxative effects in 5 instances.

The character of the stools varied. In some instances it was hard; in others it was soft; and in still others, watery. The loose watery stool was not confined to the larger doses, although the larger doses seemed to account for a larger number of the loose stools.

Disagreeable effects occurred after 10 of the 65 doses. There were slight cramps in 4 cases, nausea in 4, diarrhea in 1, and vomiting in 1. These effects occurred, for the most part, after doses of 15 Gm. or higher.

The urine was examined in a manner similar to that in the animal experiments, after 45 doses of sodium fumarate, and in the case of 26 of these doses, before administration of the drug. The results gave no indication of renal damage.

The serum N. P. N. was determined in 16 instances before and in 38 instances after the administration of fumarate. There were no changes which could be attributed to renal damage as a result of the administration of the drug. In one patient (case 24) there was a microscopic hæmaturia and an N. P. N. of 57 before administration, and values for the N. P. N. of 58 and 47 after administration. In one patient (case 18) the N. P. N. before the drug was 25 Mg. After a dose of 5 Gm., the N. P. N. remained at 25 mg., but after a subsequent dose of 15 Gm., the N. P. N. rose to 39 mg. This rise was in all probability not the result of fumarate poisoning, since this patient had congestive heart failure which was showing signs of progression before and during the experiment.

DISCUSSION

The literature on the toxicity of fumaric acid and its salts is meager. Hermann, *et al.* (1938) (5), found that an approximately 0.7 per cent solution of free fumaric acid injected slowly, intravenously, proved fatal in a dose of 0.47 Gm. per Kg. in rabbits. Death was preceded by a marked fall in the plasma pH, and it is possible that the death was due to the hydrogen ion rather than to the fumarate ion. This, however, is substantially similar to the doses which proved fatal in our experiments. Krebs, *et al.* (1938) (6), observed no ill effects from the slow intravenous injection of 1.1 Gm. of a 2.3 per cent solution of partially neutralized fumaric acid per Kg. in a rabbit. Orten, *et al.* (1937) (7), observed no toxic effects from the intravenous injection of 0.35 Gm. of a 5 per cent solution of sodium fumarate per Kg daily for 3 days in the dog. Ponsford, *et al.* (1932) (8), found the oral dose much less potent in rats since no toxic effects were observed with doses of approximately 17 Gm. of ammonium fumarate per Kg. Our own experiments show that the intravenous injection of sodium fumarate in rabbits is toxic, and proved fatal in one experiment in a total dose as low as 0.25 Gm. per Kg., although the susceptibility to this compound varies greatly; other rabbits survived much larger doses.

We have no knowledge regarding the absorption of fumaric acid. Our experiments in animals were made, therefore, with the intravenous injection, since this simulates complete absorption and provides the most severe test of systemic toxicity. Little nephropathic action was observed after single doses as high as 0.5 Gm. per Kg. and after total amounts from repeated injections, as high as 3.0 Gm. per Kg. The nature of the histological abnormality left the matter open to doubt as to whether any of the changes in the kidney could be attributed to the specific action of the fumarate. In man, we found that single doses as high as 30 Gm. and repeated doses totaling 90 Gm. (0.6 Gm. per Kg. and 1.8 Gm. per Kg. for a 50-Kg. person) produced no changes in urine or blood suggesting nephropathic action.

By comparison with these observations, the nephropathic action of tartaric acid is very high. In our experiments an intravenous dose of 0.2 and 0.3 Gm. of tartaric acid per Kg. caused marked renal effects in the rabbit and the cat. This is in agreement with the findings of Rose (1924) (4) and of Underhill, *et al.* (1914) (9); 1931 (10). The latter authors reported even smaller doses, as low as 0.05 Gm. per Kg., to be nephropathic in the rabbit.

Precise data concerning the toxicity of tartrates in man do not exist. Post (1914) (11) observed no urinary changes in 9 patients following the administration of single doses of 4 to 24 Gm. Connio (1910) (12) reported 2 cases of fatal poisoning in man with severe nephropathy after doses of 50–60 Gm. of tartaric acid, approximately 1 Gm. per Kg. for an average person.

The average dose of tartrate in a Seidlitz powder taken as a laxative is somewhat less than 10 Gm.,

Table IV.—Laxative Effect of Sodium Fumarate in Man

	Case	Time since Last Bowel Movement (Hrs.)	Dose (Gm.)	Laxative Effect: Yes or No	Laxative Effect: Time	Type of Bowel Movement	Disagreeable Effects	Blood N. P. N. Before	Blood N. P. N. After
1	A. D.	48	15	No	46	Normal	None	..	23 (65)[a]
2	A. E.	48	5	Yes	17	Hard to watery in 6 days	Delayed diarrhea	30	29 (120)
3	M. A.	48	15	No	40	....	Nausea, belching, regurgitation	32	21 (120)
4	R. B.	48	10	No	24	....	None	..	...
5	G. B.	48	10	Yes	13	Hard; moderate amount	None	..	...
6	S. A.	87	10	Yes	9	Hard	None	..	21 (45)
7	M. C.	24	5	Yes	9	Normal	None	28	26 (84)
8	R. S.	79	15	Yes	7	Hard, copious	Slight cramps (2 days later)	24	23 (40)
9	H. D.	46	15	Yes	9	Hard to soft	None	21	22 (16)
10	S. M.	53	10	Yes	19	Normal	None	..	...
11	R. L.	48	15	No	28	....	Vomiting (in 2 hrs.)	27	16 (36)
		48	15	No	45	....	None		
12	J. P.	48	10	Yes	13	Hard to soft in 4 days	None	28	28 (96)
		31	15	Yes	13	Soft	None	..	23 (15)
13	S. F.	61	15	No	48	....	None	25	27 (10)
		37	15	No	24	....	None	..	31 (36)
14	R. O.	54	20	No	49	....	Nausea	..	22 (17)
		34	15	No	24	....	None	..	23 (36)
15	A. P.	24	5	Yes	17	Hard; moderate amount	None	25	23 (96)
		43	15	Yes	5	Soft	None	..	24 (15)
		47	15	Yes	1	Normal	None	..	...
16	J. S.	24	10	Yes	7	Hard; moderate amount	None	38	33 (120)
		41	15	Yes	8	Hard; moderate amount	None	..	...
		43	20	Yes	6	Soft	None	..	...
17	M. B.	72	15	No	48	....	None	..	...
		31	15	No	29	....	None	..	...
		64	25	No	54	....	None	..	...
18	G. Ba.	24	5	Yes	5	Hard to soft (3 days)	None	25	25 (17)
		41	15	Yes	1	Soft; semi-solid	None	..	39 (36)
		52	10	Yes	1½	Soft; semi-solid	None	..	...
19	R. Br.	72	10	No	28	Hard with straining	None	..	18 (16)
		21	15	No	24	....	None	..	19 (40)
		60	25	No	24	....	Slight nausea	..	15 (12)
20	E. A.	48	10	Yes	11	Hard; moderate	None	24	20 (45)
		84	20	No	24	....	Cramps	..	18 (12)
		57	30	No	25	....	Slight nausea	..	...
21	A. R.	48	15	Yes	6	Soft; solid	None	..	21 (40)
		48	15	No	20	....	Slight cramps	..	23 (15)
		68	10[b]	Yes	5	Watery	None	..	...
		35	20	No	46	Normal, copious	None	..	...
22	P. S.	44	10	Yes	1	Watery	Diarrhea	19	19 (16)
		37	5	No	18	....	None	..	20 (12)
		55	5[b]	No	24	....	None	..	...
		29	10	No	24	....	None	..	...
23	A. S.	60	10	No	18	....	None	23	25 (85)
		78	10[b]	Yes	18	Hard to soft (3 days)	None	..	...
		46	15	Yes	15	Hard to soft (3 days)	None	..	...
		45	25	Yes	17	Normal	None	..	...
24	E. S.	90	10	Yes	18	Hard; little	None	57	58 (45)
		40	20	No	24	....	None	..	47 (36)
		33	15	No	24	....	None	..	...
		46	25	Yes	2	Soft	None	..	...
		66	30	No	39	Hard	None	..	...
25	B. F.	87	10	No	27	....	None	..	15 (18)
		114	10[b]	Yes	3	Soft	None	..	17 (36)
		46	15	Yes	22	Very hard	None	..	14 (12)
		28	15	Yes	15	Soft	Slight cramps	..	...
		24	15	Yes	21	Normal	None	..	...
		32	25	Yes	2	Soft	None	..	...
26	T. S.	35	5	Yes	21	Normal	None	22	18 (45)
		42	10	Yes	6	Normal	None	..	18 (60)
		46	10	Yes	5	Hard	None	..	16 (12)
		28	15	Yes	14	Normal	None	..	...
		30	25	Yes	11	Soft to semi-solid	None	..	...
		69	25	Yes	3	Soft	None	..	...

[a] Numbers in parenthesis designate the hours after dose when the test was done.
[b] This dose was given immediately after the time designated for the failure of the previous dose.

although not infrequently a double dose, or about 20 Gm., of tartrate is taken. Underhill, *et al.* (1931) (13), observed that after oral administration, a person may absorb as much as 20 per cent of the dose, which in the above case would be 4 Gm. or 0.08 Gm. per Kg. for a 50-Kg. person. This is close to the dose of tartaric acid which may cause injury in the kidney in rabbits (0.05 Gm. per Kg.). The validity of this comparison depends, of course, on the relative susceptibility of the human and rabbit kidney to injury by the tartrates, but concerning this point there are no data.

The use of tartrates in laxative doses apparently does not result in acute renal injury. In any case, we are not aware of any such reports. Nevertheless, in view of the foregoing relationships, the possibility cannot be excluded that the continued use of doses of tartrates which make available to the kidney amount of the order of 0.08 Gm. per Kg. may result in kidney injury which may not be revealed unless suitable long range experiments are devised for this purpose.

Our experiments in man show that sodium fumarate is an effective laxative, and by comparison with the tartrate possesses negligible nephropathic action.

SUMMARY AND CONCLUSIONS

1. Experiments in 22 animals (rabbits and cats) were carried out to study the toxicity and nephropathic activity of sodium fumarate when administered by the intravenous route. The effects were compared with those of sodium chloride and sodium tartrate.

2. The susceptibility of rabbits to sodium fumarate injected intravenously varies greatly. A single dose of 0.5 Gm. per Kg. or higher may be toxic and fatal. Occasionally a smaller dose may prove fatal. On the other hand, repeated injections of 0.5 Gm. totaling 3.0 Gm. over a period of about two weeks may be without ill effects.

3. The study of the kidneys by means of changes in blood N. P. N., creatinine, P. S. P. excretion, urine and histological examination of post-mortem sections shows that the nephropathic action of sodium fumarate is negligible by comparison with that of tartrate.

4. The laxative effect of sodium fumarate was studied in a group of 26 patients suffering from constipation. Oral doses of sodium fumarate, 5 to 30 Gm., produced satisfactory laxative effects within an average of 10 hours after administration. Examination of the urine and blood N. P. N. failed to show any signs of renal damage in this group of patients.

5. The comparison of tartrate and fumarate as laxatives in relation to the possibility of nephropathic action is discussed.

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