

may possess is therefore masked by the effects of excessive fluid, hypertonicity, acid, or alkali. The indications are that the

succinate ion is substantially inert, and doubt remains as to whether it exerts any specific toxic effects.

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Laxative Action of Succinates in Man*†

By LEON J. WARSHAW and HARRY GOLD

The laxative effect of 260 10-Gm. doses of succinic acid, sodium succinate, and magnesium succinate administered to 30 patients suffering with chronic constipation is reported. No nephrotoxic action was noted upon prolonged administration. A dosage form is suggested to overcome the unpleasant effects sometimes experienced by the ingestion of simple solutions of succinates in water.

IN A PREVIOUS study (1), a method was described for the evaluation of laxative agents in constipated human subjects. This method and modifications of it were used in observations on the laxative properties of gluconates (2), fumarates, tartrate, and citrate (1, 3). Several carboxylic acids and their salts are known to possess laxative properties, and some of them, notably tartrates, are nephrotoxic. There are several isolated observations indicating that the succinates possess little, if any,

toxicity in man, and a recent study in cats (4) shows that succinic acid, sodium succinate, and magnesium succinate are substantially free of toxic actions which cannot be ascribed to excessive fluid, acidity, or alkalinity. This study shows that large doses of these compounds, the equivalent of about 30 Gm. for a man, frequently produce vomiting and/or diarrhea in cats.

The present report deals with the results of a study designed to test the laxative properties of the succinates in constipated ambulant human subjects. There are also observations relating to the toxicity of the succinates in man.

EXPERIMENTAL

The subjects used were ambulant adult patients who had been in regular attendance at a cardiac clinic for periods varying from several months to several years. Many of these patients required maintenance doses of drugs for their cardiac condition but only those whose heart disease and state of compensation were relatively stable were selected. The basis for their assignment to this study was functional constipation with a long history of dependence upon laxatives. The agents that had

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been used were Epsom salts, Seidlitz powders, cascara, milk of magnesia, or phenolphthalein preparations. The character of the constipation was such that a laxative was found necessary at least twice weekly, some patients having become accustomed to a daily dose of a laxative. When they failed to take it, several days would elapse without a bowel movement.

water followed by one-half glassful of water. The plan was to have the drug approximately isotonic in the gastrointestinal tract.

A simple record form was issued at every clinic visit made at intervals of one or two weeks. It contained the following rubrics: Day of the week, time medicine was taken, time of bowel movement, kind of bowel movement, and any other symptoms.

TABLE I.—LAXATIVE EFFECTS OF SUCCINATES

	Succinic Acid	Sodium Succinate	Magnesium Succinate	Total
No. patients	24	10	8	30 ^a
No. doses	128	100	32	260
No. "positive results"	70 (54%)	84 (84%)	26 (81%)	180 (69%)
Time to effect				
Average	9.8 hr.	6.0 hr.	5.4 hr.
Range	1-24 hr.	1-24 hr.	1-11 hr.
Vomiting				
No. patients	8 (33%)	4 (40%)	4 (50%)	14 ^a (47%)
No. doses	15 (12%)	14 (14%)	6 (19%)	35 (13%)

^a These numbers are smaller than the sum of the columns because some patients were used for more than one drug.

TABLE II.—COMPARISON OF SUCCINATES IN THE SAME PATIENT

Patient	J. T.	M. S.	S. Y.	F. S.	M. G.	M. B.	F. L.	B. K.
	Succinic Acid							
Dose, Gm.	10	10	5, 10	10	10	10	10	..
No. doses	14	2	5 each	3	9	2	6	..
No. "positive responses"	9	1	10	1	9	1	5	..
Time to response, hr.	17 (4-23)	5	5 (2-12)	3	5 (1-12)	..	8 (5-12)	..
Vomiting, No. doses	0	1	0	0	1	0	0	..
	Sodium Succinate							
Dose, Gm.	10	10	10	10	10	10	10	10
No. doses	5	1	10	4	22	5	17	29
No. "positive responses"	4	1	9	0	22	5	17	26
Time to response, hr.	23 (22-24)	9	6 (1-18)	0	3 (2-9)	3 (2-4)	2 (1-8)	8 (2-14)
Vomiting, No. doses	0	0	0	4	0	0	0	3
	Magnesium Succinate							
Dose, Gm.	..	10	10	10	10	10
No. doses	..	3	2	2	3	8
No. "positive responses"	..	3	2	0	3	8
Time to response, hr.	..	8 (7-8)	2 (1-2)	0	4 (3-4)	10 (7-11)
Vomiting, No. doses	..	0	0	2	1	0

The patients were instructed to take the agent under investigation, following the lapse of at least twenty-four hours after the expected daily bowel movement. In the majority of cases, it was taken in the morning. If twenty-four hours then elapsed without a bowel movement, the dose was presumed to have failed and the patient was instructed to take a soap-suds enema. The dose was not repeated for at least forty-eight hours following the enema, since an enema itself often interferes with the subsequent action of a laxative.

The compounds—succinic acid, sodium succinate, and magnesium succinate—were dispensed in powders containing 10 Gm. each, in a few instances 5 Gm. The dose was taken dissolved in one glass of

The patient filled out this form for each dose, and returned it during the subsequent clinic visit. A large proportion of the patients were familiar with this technic of observation and recording, having served as subjects in previous studies of this type.

RESULTS

Table I summarizes the results with the entire group of 260 doses in 30 patients. The number of doses taken by the individual patient varied from 1 to 37, average 6 doses. All the patients developed a laxative effect after one dose or another, and such a result occurred after nearly three-fourths of the doses in an average period of seven hours with wide variations of from one to twenty-four hours.

Minor unpleasant symptoms were very frequent, nausea, epigastric discomfort, diarrhea, and abdominal cramps. Vomiting was produced in about one-half of the patients and after about one-sixth of the doses. No conspicuous difference was in evidence among the 3 preparations with respect to laxative activity or disagreeable symptoms, the differences seen in the table being probably due to the relatively small numbers and wide variations in individual responses.

In Table II are summarized the results with 157 doses in 8 patients who received either 2 or all 3 preparations. It may be noted that in these the incidence of laxative responses and of vomiting are of the same order for each of the 3 preparations.

While there are some suggestive observations in the literature indicating a mild nephrotoxic action of succinates in rabbits, the study in cats (4) failed to disclose any such action after very large doses. In 9 subjects who received from 4 to 37 oral doses of 10 Gm. each of the succinates, the urine was examined for specific gravity, albumin, casts, and blood cells, and the blood for nonprotein nitrogen. All 3 preparations were represented. A specimen was taken before the study was started and again after the last dose. There were no significant changes in the urine. The results of the blood NPN values are summarized in Table III. While the

TABLE III.—EFFECT OF SUCCINATES ON BLOOD NPN

Patient	No. Doses	NPN, Mg. %	
		Before	After
B. K.	9	39	41
J. B.	10	39	40
J. T.	19	32	34
B. M.	13	31	35
S. Y.	22	37	34
M. G.	34	42	29
B. R.	13	31	46
L. G.	4	29	36
B. K.	37	43	30

values are sometimes higher after the drug than before, the reverse is often the case, and there is no significant trend.

The unpleasant symptoms appear to be due to local action involving taste and irritation. Succinic acid is quite sour; sodium succinate produces an immediate sense of coolness and is faintly bitter; magnesium succinate produces an immediate sense of heat with a stronger bitter taste and appears to be the most unpleasant of the 3. The dose of 10 Gm. used in most cases of this study appears to be larger than the average required dose since all patients responded at one time or another, and the laxative response for the total number of doses was 69%. In the practical application of the succinates as laxative agents, smaller doses to test the patient's sensitivity, larger volume of water with each dose, or a preparation in an effervescent form, may help to solve the problem of unpleasant reactions.

SUMMARY

Succinic acid, sodium succinate, and magnesium succinate, administered in doses of 10 Gm. to 30 patients suffering with chronic constipation, produced a laxative effect after an average period of about 7 hours in approximately three-fourths of 260 doses tested. The prolonged use of such doses of succinates appeared to be without nephrotoxic action in man as judged by the urine and blood NPN. Such doses administered in one and one-half glassfuls of water caused frequent unpleasant effects including vomiting. No significant difference with respect to laxative activity or disagreeable side effects among the 3 preparations was in evidence. A suggestion is made concerning a possible means for controlling the unpleasant effects in the practical application of the succinates as laxative agents.

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