A Method for the Evaluation of Laxative Agents in Constipated Human Subjects, with a Study of the Comparative Laxative Potency of Fumarates, Sodium Tartrate and Magnesium Acid Citrate*

By Harry Gold and William Zahm†

The comparative potency of laxative agents has been extensively studied in lower animals. The results are, for the most part, not applicable to humans because of the differences in the reaction of various species to laxative drugs, although more recent observations show that the rhesus monkey is a suitable animal for the study of several cathartic agents (1). Human subjects with constipation should obviously yield the most direct answer to questions relating to the comparative potency of laxative agents, but, strange as it may seem, systematic comparisons in humans are almost entirely wanting.

In the present paper we describe a method for the comparison of laxative agents in constipated human subjects. The criterion for relative potency on which most reliance was placed in this study was the incidence of positive responses to a series of doses, although in the further development of the method other criteria may be added. The most precise results are secured in those cases in which all the agents are compared in one and the same person.

This method was applied in a comparative study of several organic acids. It is well known that the salts of organic acids exert a laxative action. Among the most popular are potassium and sodium tartrate (Rochelle salt, Seidlitz powders) and magnesium citrate. Gluconic acid also produces laxative effects (2, 3) in doses of 10 Gm. or more. In a previous study (4), it was found that the nephrotoxic action of fumarate in animals is negligible by comparison with the tartrate, and preliminary observations with 65 doses in 26 bed patients showed a laxative effect after 59% of the doses ranging from 5 to 30 Gm. In view of the foregoing, this study was planned to explore further the efficacy of the fumarates as laxative agents in man.

Supplementary observations on the nephrotoxic action of tartrates in cats are included.

EXPERIMENTAL

The subjects used were ambulant patients who had been in regular attendance at our clinics during periods varying from several months to several years. They were under regular social service supervision. Most of them had heart disease among other health problems. They were selected from a total case load of approximately 1500 patients. The first basis for their selection in this study was chronic constipation. There was, in all cases chosen, a long history of dependence upon a laxative such as cascara, senna, phenolphthalein, Epsom salts, milk of magnesia or mineral oil. The constipation was functional. Further classification of the constipation was not made, since that was not essential in a study of the relative potency of compounds. Its character was such that a laxative was found necessary at least twice a week, *i. e.*, it was the patient's experience that at least twice a week the daily bowel movement failed to take place at the expected time and it was their practice to secure a movement by means of a laxative agent taken at bedtime of that day or the following morning. A few subjects were included who required a laxative only once a week, and also a few in whom constipation was so obstinate that a laxative was used daily.

The laxative agent under investigation was taken following the lapse of several hours after the expected daily bowel movement (always 24 hrs. or longer since the last bowel movement). In the majority of cases it was taken in the morning. This secured a more satisfactory record of the period required for its effect. A few subjects preferred it at bedtime.

A simple record form was issued at every clinic visit made at intervals of 1 or 2 weeks. It contained the following rubrics: day of the week, time medicine was taken, time of the bowel movement, kind of

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bowel movement (normal, loose, hard, watery). The patient filled this out at the time and returned it during the subsequent visit to the clinic.

Five compounds were studied: sodium fumarate, magnesium fumarate, calcium fumarate, sodium tartrate and magnesium acid citrate. They were dispensed in powders containing 10 Gm. each, and in quantities sufficient to last 1 or 2 weeks in different cases. The powder was taken dissolved in one-half glass of water followed by one-half glass of water. Calcium fumarate and magnesium fumarate are not very soluble and made a slightly bitter partial suspension. The remaining 3 compounds made a clear salty solution.

The plan of the study involved the assumption that if a patient took a fixed dose of a laxative agent for constipation, and repeated the dose as the conditionally the positive result occurred within a few minutes, in a few cases nearly 24 hrs. elapsed. There is a strong probability that in the first case the effect resulted from a reflex rather than from the direct action of the agent, and in the second case the bowel movement may have been unrelated to the drug. The possibility of spontaneous bowel movement after the drug, independent of any drug action, is always there. We have not determined how great a source of error this might be, but since the number of cases is large and such an error should apply equally to all the preparations, it is probably of no importance in the deductions regarding the relative potency of the various compounds.

The 10-Gm. dose was selected for this study, since preliminary observations with fumarate (4) showed that it was not uniformly effective and yet gave a

TABLE I.—ILLUSTRATIVE TYPE OF DATA

Order of Doses Drug	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
						Patient N. M.										
Sodium fumarate	0[a]	7.5	0	0	0	0	0	2	1.5	1.5	...	...	...	...	...	...
Calcium fumarate	3	3	3	3	3	3	0	2.5	2.5	...	...	...	...	...	...	...
Magnesium fumarate	1.5	1.5	1.5	2	2	2	1.5	1.5	1.5	1.5	2	2	...	...	...	...
Sodium tartrate	1.5	1.5	1.5	1	1	1	1	1	1	...	...	...	...	...	...	...
Magnesium acid citrate	2.5	0	2.5	0	1.5	1.5	2	2	2	0	1.5	2	...	...	...	...
						Patient A. J.										
Sodium fumarate	1	7	18.5	1.5	4	0	2	2	11	...	...	...	...	...	...	...
Calcium fumarate	8	4	2	17	3	5	16	1	12	...	...	...	...	...	...	...
Magnesium fumarate	0	4	3	1	3	7	2	5	3	1	3	4	10	...	...	...
Sodium tartrate	0	3	10.5	3	2.25	20	6	8.5	2.5	3	...	...	...	...	...	...
Magnesium acid citrate	6	1	1	3	4	13	1	4	5	12	5	4	...	...	...	...
						Patient M. S.										
Sodium fumarate	12	1.5	1.75	3.5	0	2.5	0	1.25	3	0	...	...	...	...	...	...
Calcium fumarate	0.5	1.25	0	6	0.3	2.5	0	4	0.75	0	0	7.5	2	0	0	1.3
Magnesium fumarate	0.6	0	1.25	1.5	0	0	0	1.5	0	0.5	0	0.5	0.5	2	...	...
Sodium tartrate	0	1.5	1.5	0	2	0	2	2	3.5	0	0	2.5	5	0	...	...
Magnesium acid citrate	0	2	0	0	0	0	0	0	0	1.5	0	0	0	0.5	1	2

[a] The zeros indicate failure of the dose; other figures indicate number of hours to a positive response.

tion recurred at intervals over a period of 3 to 4 weeks, the incidence of positive responses to the dose would vary with the potency of the laxative agent. While we have not determined the sensitiveness of the method or the character of the dosage-response curve for the agents in question, there is sufficient general experience to insure the fact that the basic assumption is valid. We have also assumed that if the standard preparation with which comparisons were to be made yielded positive responses considerably below 100%, practical differences in the potency which might exist between the compounds under investigation would be disclosed.

The response was considered positive if the bowel movement took place within 24 hrs. after the dose. There is here without doubt a source of error. Occa- fairly high incidence of positive responses. In the case of potassium and sodium tartrate, 10 Gm. has been established as the average laxative dose on the basis of general experience. A smaller dose might have been nearer to the more sensitive part of the dosage-response curve, but might also create a more difficult problem, since it would not be feasible to carry out protracted experiments in patients with a dose of a laxative agent which was too often ineffectual.

RESULTS

The study was started with 256 subjects. Since fairly rigid criteria were maintained for their continued service, a great many were dropped for various reasons and the final analyses were made from the results obtained with 140 subjects, or 55% of the

original group. The remaining 45% were discontinued for such reasons as these: inability to keep an accurate record, inability to write English, preference for their customary laxative, prejudice against the use of a powder, periods of constipation too irregular, etc. Among the final group both sexes were represented and the ages ranged from 23 to 76 years, average 56.6 years. It should be noted that these patients constitute a very satisfactory group of subjects for long-range studies on ambulant patients. A large proportion of them were familiar with the technique of coöperation in long-period systematic treatments, having served as ambulatory patients in the studies of the xanthines and digitalis, in which they had grown accustomed to reporting effects systematically and accurately.

Table I shows the type of data in 3 representative cases. Each of these patients received a series of doses of each of the 5 compounds. In some cases, one agent produced more positive responses, while in other cases the incidence of positive results was essentially similar for all agents.

the beginning to the end of the study. The patients received the compounds in average series of 7.39 to 8.85 doses. The incidence of positive responses for the different compounds varied from 69.8% to 81.8% of the doses given, when computed directly from the total number of doses and the total number of positive responses, and the time required for the effects varied between an average of 5.45 and 7.03 hrs.

There is the possibility that the order of sensitiveness to the different compounds might differ from person to person. However, the experiments were not designed to establish this point.

In order to determine whether these differences are significant, the data have been subjected to more detailed statistical analysis for which we are indebted to Dr. C. I. Bliss. The statements which follow are based on his findings.

For the incidence of positive responses, the analysis was based only on cases with 4 or more doses of any one agent. The results are presented in Table III. The patients were divided into 2 groups: Group I represents 13 patients who received all 5 drugs and in whom the reactions were neither all positive nor all negative to all drugs; Group II represents the additional patients tested with 1 to 4 of the drugs, including also those with all positive or all negative responses to the 5 drugs (4 such patients).

There were 17 patients who were tested with all 5 agents. Four of these patients were omitted from

TABLE II.—SUMMARY OF EFFECT OF 10-GM. DOSES OF 5 LAXATIVE AGENTS IN A GROUP OF 140 PATIENTS

Drug	No. Patients	Total No. Doses	Average No. Doses per Patient	Results No. Pos.	Results No. Neg.	Results % Pos.	Time (Hrs.) for Pos. Result Range	Time (Hrs.) for Pos. Result Average
Sodium fumarate	93	688	7.39	493	195	71.6	0.08–23.50	6.90
Calcium fumarate	61	451	7.39	315	136	69.8	0.33–23.75	6.46
Magnesium fumarate	61	540	8.85	442	98	81.8	0.33–22.00	6.09
Sodium tartrate	43	379	8.81	308	71	81.3	0.50–23.75	5.45
Magnesium acid citrate	38	335	8.81	264	71	78.8	0.50–23.50	7.03

TABLE III.—ANALYSIS OF DATA RELATING TO THE INCIDENCE OF POSITIVE RESPONSES WITH THE 5 LAXATIVE AGENTS

Group		Sodium Fumarate	Calcium Fumarate	Magnesium Fumarate	Sodium Tartrate	Magnesium Acid Citrate
I	Average no. of doses per patient	12.3	11.8	12.8	11.8	12.0
	Percentage of 13 patients with no failures	23.1	30.8	30.8	38.5	46.2
	Mean[a] percentage of positive responses for all 13 patients	72.7	75.6	79.3	78.3	81.7
II	Total number of patients	57	37	43	26	22
	Percentage of patients with no failures	38.6	37.9	55.8	61.5	54.5
	Percentage of patients with all failures	14.0	13.5	11.6	7.7	18.1
	Number of patients with some failures	27	18	14	8	6
	Mean[a] percentage of positive responses, based on patients with some failures	65.4	53.5	68.6	65.6	57.1

[a] Mean of percentages for each patient, each weighted by square root of number of doses of each drug.

While it would have been most desirable to make all comparisons in one and the same person, such comparisons proved feasible in only a small number of the total group. In Table II are summarized the results with the entire group of 2393 doses in 140 patients. The number of doses taken by the different patients varied greatly. Some of them took only 1 dose, others took as many as 100 doses from

Group I, one because none of the doses produced a positive reaction, and the other 3 because all doses were effective. The variance between patients was over 5 times the error variance and highly significant, indicating the importance of balancing differences between individuals in such experiments. Because of this, the averages in Table III were computed from the percentages for each patient rather than from the total number of doses and the total number of positive responses, weighting each percentage so as to compensate approximately for the differences between the number of doses per patient, which varied for a single drug from 4 to 26. Differences in the incidence of positive responses between the 5 drugs in these 13 patients were not significant when tested in an analysis of variance.

for a rising incidence of patients with no failures, running parallel with a slightly rising incidence of positive results as one reads across from sodium fumarate to magnesium acid citrate. This suggests that there may be some difference in the potency of the group of agents studied, but the difference is so small that in an analysis of variance of our data, as already indicated, it is not significant. The reverse order of some of these differences in Group II of Table III further suggests that no substantial difference in the potency of these compounds exists.

The data concerning the length of time required for the laxative effects for the 5 compounds have been similarly analyzed. The length of time for an effect might also be used as a criterion for comparing the potency of laxative agents. From some stand-

TABLE IV.—ANALYSIS OF DATA RELATING TO THE TIME REQUIRED FOR THE POSITIVE RESPONSES WITH THE 5 LAXATIVE AGENTS

Group		Sodium Fumarate	Calcium Fumarate	Magnesium Fumarate	Sodium Tartrate	Magnesium Acid Citrate
I	No. of patients with all doses positive	6	7	7	8	9
	No. of patients with some failures	10	9	9	8	7
	Mean[a] time in hours in patients with all doses positive	3.30	4.11	4.90	3.61	4.35
	Mean[a] time in hours in patients with some failures	7.06	5.93	4.48	5.74	6.05
	Mean[a] time in hours in all patients	5.05	4.90	4.68	4.52	4.98
II	No. of patients with all doses positive	22	13	25	14	10
	No. of patients with some failures	20	13	11	7	4
	Mean[a] time in hours in patients with all doses positive	2.71	4.52	3.83	3.85	5.04
	Mean[a] time in hours in patients with some failures	6.54	5.73	5.95	4.58	9.71

[a] Geometric means based on average for each patient and drug, weighted by square root of number of positive responses in each individual average.

In Group II, which consists of the additional series of patients tested with from 1 to 4 of the drugs, the "sensitive" patients who always responded and the "insensitive" ones who always failed to respond have been listed separately and excluded from the calculation. The mean percentage of positive responses for the different drugs was computed only from those patients in whom the incidence of positive responses fell between the foregoing extremes. Because individual differences could be only partially balanced at best in this series, the results are more irregular, despite the larger number of patients.

As already stated, the chief criterion for comparing the potency of the 5 laxative agents was the incidence of positive responses to a fixed dose. It is possible, however, that other criteria might be used, such as the percentage of patients who will show all failures or no failures in response to a fixed dose of the various agents. In Table III a comparison of the column of figures for the percentage of patients with no failures in Group I with that showing the mean percentage of positive responses, reveals 2 parallel trends, a tendency

points this criterion possesses advantages as a quantitative index of potency over the criterion of percentage of positive responses. The results are presented in Table IV. Here again the patients were divided into 2 groups: Group I includes those patients in whom all 5 agents were used; Group II comprises additional patients in whom 1 to 4 of the agents were used. The analysis of variance shows that there is no difference between the 5 drugs used with respect to the length of time that elapsed between the dose and the laxative effect. This analysis was made in the case of the 16 patients (Group I) who were tested with all 5 drugs. The variability between patients is again very large, larger than in the case of the other criterion (percentage of positive responses), its variance being here more than 42 times as large. With this criterion, it is therefore especially important to balance differences between patients. Exclusive of differences between patients, the correlation between the percentage of positive responses and the mean log-time was small and not significant ($r = 0.211$, $M = 47$). Despite this

TABLE V.—TYPES OF STOOLS WITH THE 5 LAXATIVE AGENTS

Drug	Total No. Positive Doses	Normal No.	Normal %	Hard No.	Hard %	Diarrheal[a] No.	Diarrheal[a] %
Sodium fumarate	493	175	35.5	184	37.3	134	27.2
Magnesium fumarate	442	187	42.3	69	15.5	186	42.2
Calcium fumarate	315	133	42.2	109	34.6	73	23.2
Sodium tartrate	308	143	46.4	52	16.9	113	36.7
Magnesium acid citrate	264	138	52.3	71	26.9	55	20.8

[a] Loose, watery or frequently repeated.

small correlation, the geometric mean interval for the laxative effect was consistently and significantly ($P < 0.01$) shorter in patients who showed a positive response to all doses than in those who showed some failures with the given drug (1 exception).

The data relating to the type of stools have been assembled in Table V. It may be noted that normal, hard, and watery or diarrheal stools are represented among the doses of all five preparations. and that the gross data indicate some significant differences in the incidence among the 5 drugs. It was not found feasible to analyze these data with respect to differences between patients, and although differences between the drugs are suggested in an analysis based on the total number of doses, it is considered unsafe to draw any inference from this analysis in view of the well-known wide differences between individuals with regard to such reactions.

TABLE VI.—DISAGREEABLE EFFECTS WITH THE 5 LAXATIVE AGENTS

Drug	Total No. Doses Administered	Nausea and/or Vomiting No.	Nausea and/or Vomiting %	Cramps No.	Cramps %	Total of Disagreeable Effects, %
Sodium fumarate	688	56	8.2	20	2.9	11.1
Magnesium fumarate	540	21	3.8	18	3.3	7.1
Calcium fumarate	451	31	6.8	9	1.9	8.7
Sodium tartrate	379	6	1.6	8	2.1	3.7
Magnesium acid citrate	335	2	0.6	11	3.2	3.8

The patient's judgments concerning the type of stool are not sufficiently precise to warrant a statistical analysis of the differences indicated in the table.

The data concerning disagreeable effects such as nausea and/or vomiting, and abdominal cramps have been assembled in Table VI. It is clear that similar disagreeable effects are produced by all 5 compounds

Nephrotoxic Action of Tartrates in the Cat.—In a previous study (4) it was shown that 300 mg. of sodium tartrate per Kg. given intravenously in a cat produced severe renal damage, as shown by the fall of the phenolsulfonphthalein excretion to zero, and marked elevation of the blood N. P. N. and creatinine. The histological sections of the kidney

TABLE VII.—EFFECT OF SODIUM TARTRATE ON THE BLOOD AND URINE IN CATS

Cat. No.	Dose Single, Mg./Kg.	Dose Total No.	Total Dose Gm./Kg.	Experimental Day[a]	Blood N. P. N., Mg. %	Blood Creatinine, Mg. %	Urine Alb. and Sugar	Urine Spec. Grav.
7	Control		...	2	33	1.4	0	...
(Original wt. = 3.0 Kg.			...	8	38	1.5	0	1.054
Final wt. = 3.1 Kg.)			...	13	36	1.5	0	1.076
			...	31	38	1.3	0	1.050
			...	47 to 48	38	1.7	0	1.046
			...	68	41	1.4	0	1.040
			...	82	42	1.6	0	1.050
			...	96	39	1.5	0	1.044
			...	110	41	1.4	0	1.050
			...	126	44	1.2	..	...
4	100	45	...	−16	43	1.7	0	...
(Original wt. = 3.0 Kg.			...	−13	40	1.6	0	...
Final wt. = 3.1 Kg.)			...	−8 to −1	39	1.6	0	1.070
			0.5	+12	38	1.1	0	1.040
			1.1	+26	53	1.7	0	1.040
			1.5	+34	54	0.9	..	...
			2.0	+46	47	1.4	0	1.058
			2.6	+61	44	1.6	0	1.045
			3.2	+75 to +77	43	1.3	0	1.036
			3.8	+89	44	1.3	0	1.050
			4.5	+105	46	1.2	..	...

[a] (−) indicates number of days before injections were started; (+) indicates number of days after beginning of the injections.

in this animal showed marked tubular degeneration. Several times that dose of sodium fumarate was without this effect. The question arose whether small doses of tartrate might not also, by frequent repetition, give rise to renal damage, even though the doses were insufficient to cause chemical changes in the blood. This question was tested in a group of 8 cats, 3 used as controls, and 5 receiving sodium tartrate. In 1 cat the dose was 50 mg./Kg., in each of 2 others 75 mg./Kg., and in each of the last 2, 100 mg./Kg. The drug was given in a 5% solution of sodium tartrate by subcutaneous injection 3 times a week for a total of 45 doses over a period of nearly 4 months. A summary of the data for a typical experiment suffices to illustrate the plan of the study and the results (Table VII).

The animals were maintained on a constant diet of the following: 150 Gm. of canned dog food 3 times a week, 150 Gm. of fresh meat twice a week and 150 Gm. of fresh liver once a week. The controls, as well as the treated animals, maintained their body weight throughout the period of study. There were no significant changes in the N. P. N. or creatinine. The animals were sacrificed at the end of the experiment. The weights of the kidneys were essentially the same for the treated and the control groups, 12 Gm. each (11 to 13.5 Gm.) for the treated, and 11 Gm. each (10 to 16 Gm.) for the controls. The kidneys appeared similar on gross examination. The kidneys of 4 animals were examined histologically. The sections of the 2 control animals were normal, while those of the 2 animals which received the 100-mg. doses of sodium tartrate showed considerable tubular degeneration. These doses for cats are substantially similar to the doses of tartrate that would pass through the kidneys of a person after a 20-Gm. dose taken orally. These results suggest a potential hazard in the continued use of tartrates as laxatives, which could easily escape detection.

SUMMARY AND CONCLUSIONS

1. A method is described for the quantitative comparison of laxative agents in constipated human subjects.

2. By this method it is shown that the laxative efficacies of the fumarates of sodium, calcium and magnesium are the same, and that these three also possess approximately the same laxative potency as sodium tartrate and magnesium acid citrate, gram for gram. A 10-Gm. dose of any of the foregoing produces a bowel movement within an average of about 6 hrs. in about 75% of the times it is used in patients in need of a laxative.

3. The fumarates provide satisfactory substitutes for the tartrates as laxative agents, without the potential nephrotoxic hazards of the tartrates.

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Pharmacologic Action of Gelsemine and Dihydrogelsemine*

By F. G. Henderson and K. K. Chen

The alkaloid gelsemine has been known for over seventy years. It has been isolated repeatedly from the roots and rhizomes of the yellow jasmine, *Gelsemium sempervirens*. Earlier reports were made by Wormley (1), Spiegel (2), Goeldner (3) and Moore (4). Chou (5), working in Paris, succeeded in obtaining three crystalline substances from an American sample of *Gelsemium sempervirens*, one of which was gelsemine. The empirical formula of the latter was found to be the same as that of Moore, namely, $C_{20}H_{22}O_2N_2$. Recently Chu and Chou (6) prepared dihydrogelsemine by catalytic reduction. A preliminary report on the pharmacology of gelsemine, based upon the work of one of us (K. K. C.), was made by Chou (5), but dihydrogelsemine has not been investigated in animals.

An unsaturated linkage sometimes has a profound influence on the pharmacologic action. For example, allyl alcohol is much more toxic than propyl alcohol. Among the digitalis-like substances a saturation of the double bond results in loss of activity

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