THE EFFECT OF A STANDARDISED SENNA PREPARATION ON THE HUMAN BOWEL

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A standardised senna preparation, was administered to 52 ward patients, in doses to each person of 1, 2, 3 and 4 tablets, and to 126 medical students in a dose of 3 tablets. Three active tablets and 3 inert tablets were also administered to each of 99 students, and one active tablet and one inert tablet to each of 44 students. With 3 tablets of senna preparation the "speed of action" with students (mean 12·15 hours) was significantly slower than with ward patients (mean 9·7 hours). In the ward patients the frequency of griping, of looseness of stool and of multiple bowel movements increased with rising dosage. In the students' trial with one tablet there was no significant difference between the results with the active and with inert tablets; one senna tablet would appear to have a negligible pharmacological effect. Thirty-nine students and 5 ward patients experienced griping in the absence of other arbitrarily defined evidence of overdosage. The incidence of anorexia and nausea is as high with inert as with active tablets. Analysis of the results showed no significant difference in response between male and female students.

Senna belongs to the anthraquinone group of purgatives and owes the greater part of its activity to two anthranol-containing glycosides which have been named sennosides A and B. In addition, other principles including a third glycoside are present and reinforce the action of the sennosides[1]. The pharmacology of senna is well reviewed by Abrahams[2]. After ingestion the sennosides are absorbed and pass into the blood stream. After chemical changes have occurred, the active principles, the emodins, reach the large bowel. Here, the propulsive movements are greatly stimulated, thus causing a rapid passage of faecal contents.

The standardised senna preparation, prepared from Alexandrian senna pods, is presented as tablets, and is also available incorporated with cocoa, malt and sugar as "granules". Two batches of tablets were used in the work described. Each tablet in the first batch contained the "total active constituents" of 250 mg. Alexandrian senna pod, B.P.: the sennoside A + B content of each tablet by chemical assay was 7·50 mg. Each tablet in the second batch contained the "total active constituents" of 200 mg. Alexandrian senna pod, B.P.: the sennoside A + B content of each of these tablets was 7·25 mg. Tablets of both batches were regarded as having the same potency for clinical purposes.

The object of the present trial was to assess the effect on bowel function, to observe the incidence and type of side-effects, and to make similar observations after giving inert tablets. The trial was conducted in two parts: in the first the drug was administered to ward patients, in the second to volunteer medical students.

The ward series consisted of 52 male patients, selected at random, but excluding the seriously or acutely ill, those with severe chronic constipation

requiring enemata, and those over 80 years. Their normal frequency of bowel movement is shown in Table I, and their normal stool consistence in Table II. At 8 a.m., immediately after breakfast, each patient received one tablet of 7·50 mg., and the following observations were made. (*a*) Time

TABLE I

NORMAL FREQUENCY OF BOWEL MOVEMENT—WARD PATIENTS AND STUDENTS

Frequency of movement	Number of patients	Number of students
Twice daily	4	32
Once daily	8	188
Twice in three days	10	26
Every second day	16	23
Less often than every second day	14	—

required for the bowels to move; (*b*) the number of bowel movements in the 23 hours after administration of the drug; (*c*) bulk, consistence and colour of the stools, and (*d*) side-effects.

This regimen was later repeated at intervals of at least 3 days using 2, 3 and 4 tablets.

RESULTS

Time of action. The time taken to act is shown in Table III(*a*).

Consistence of stool. None of the patients in the trial gave a history of recent loose bowel movements. Stool consistence in relation to dose is shown in Table IV(*a*).

TABLE II

NORMAL STOOL CONSISTENCE—WARD PATIENTS AND STUDENTS

	Firm	Soft	Loose
Number of patients	42	10	—
Number of students	211	58	—

Number of bowel movements. No patient had more than four bowel movements in the 23 hours after the administration of the tablets in any dosage. Details are set out in Table V(*a*).

Bulk and colour of the stools. No changes in bulk or colour of the stools were noted.

Side-effects. Two patients had anorexia after 4 tablets, one patient after 3 tablets. None experienced nausea or vomiting.

Griping. Results are set out in Table VI(*a*). Of those who had griping with the larger doses, 4 and 3 tablets, 5 in each case had not more than two bowel movements, neither of which was loose. No other side-effects were noted.

Trial with Student Volunteers

This was in three stages, with a total of 208 male and 61 female volunteers, with ages from 19 to 35 years: all but 68 were under 23 years. The tablets were swallowed immediately before retiring to bed and

observations were recorded on a form. The normal frequency of bowel movement is shown in Table I, and the normal stool consistence in Table II. None of the students had used a laxative regularly, and only 9 of the 208 men and 4 of the 61 women had used a laxative intermittently. In the first stage, 3 tablets (7·50 mg.) were administered to 96 male and 30 female students.

RESULTS

Time of action. This is shown in Table III(*b*). One woman and 5 men were awakened from sleep by the call to stool. Six women and 29 men had a first bowel movement before breakfast.

TABLE III

MEAN INTERVALS BETWEEN MEDICATION AND FIRST BOWEL MOVEMENT

		Mean interval hours	S.D.
(*a*)	*Ward trial:*		
	Senna preparation tablets (7·50 mg.)		
	1 tablet	12·8	9·43
	2 tablets	12·2	8·01
	3 "	9·7	6·43
	4 "	8·6	5·53
(*b*)	*Student trials:*		
	3 senna preparation tablets (7·50 mg.)		
	96 men	11·79	2·74
	30 women	11·63	6·41
	Total 126 students	11·75	4·02
(*c*)	3 senna preparation tablets (7·25 mg.)		
	75 men	12·49	5·2
	24 women	13·12	10·6
	Total 99 students	12·65	6·8
(*d*)	3 inert tablets 99 students	17·18	11·96
(*e*)	1 senna preparation tablet (7·25 mg.) 44 students	16·05	8·51
(*f*)	1 inert tablet 44 students	15·75	10·04

Consistence of stool and number of bowel movements. The consistence of the first stool is shown in Table IV(*b*): in none was the stool firmer than normal. In addition to those whose first stool was loose, 30 men and 14 women whose first stool was firm or soft had a second or subsequent loose stool: thus 67 men, 70 per cent, and 19 women, 63 per cent, had at least one loose stool after the tablets. The number of bowel movements experienced in the 23 hours after the senna preparation is shown in Table V(*b*).

Bulk and colour of the stools. No change in stool colour was noticed. Of the women, 22 noticed no change in bulk of the first stool, 6 thought it was increased, and 2 reported a decrease. Fifty-seven men noticed no change in bulk of the first stool, 29 thought the bulk was increased and 10 thought it decreased.

Side-effects. Three female and 7 male students experienced anorexia; 4 female and 8 male felt nauseated; and one male student vomited during the day after taking the drug although he attributed the vomiting to dietary indiscretion.

Griping. Results are set out in Table VI(*b*). There was no correlation of griping and increased bowel evacuations nor of griping and the occurrence of loose motions. But, of the 51 men and 20 women who experienced mild griping, 5 men and 2 women had one or two bowel movements only, neither of which was loose; and of the 15 men and 3 women who experienced moderate or severe griping, 7 men and 3 women similarly had one or two bowel movements only, neither of which was loose.

In the second and third stages of the trial with students, inert control tablets, identical in apperarance, but composed of powdered dried grass,

TABLE IV

STOOL CONSISTENCE WITH VARYING MEDICATION

		Number of subjects whose first movement after medication was			Total No. who had a loose bowel movement at any time in the following 24 hours
		Firm	Soft	Loose	
	Ward trial:				
(*a*)	Senna preparation tablets (7·50 mg.)				
	1 tablet	35	13	4	6
	2 tablets	8	26	18	20
	3 "	8	18	26	29
	4 "	0	22	30	34
	Student trials:				
(*b*)	3 senna preparation tablets (7·50 mg.)				
	96 men	20	39	37	67
	30 women	11	14	5	19
	Total 126 students ..	31	53	42	86
(*c*)	3 senna preparation tablets (7·25 mg.)				
	75 men	17	38	30	45
	24 women	3	13	8	17
	Total 99 students ..	20	51	38	62
(*d*)	3 inert tablets 99 students ..	61	33	5	9
(*e*)	1 senna preparation tablet (7·25 mg.)				
	44 students ..	24	17	3	7
(*f*)	1 inert tablet 44 students ..	32	10	2	5

sugar, starch and cocoa, were used. The students were told that all the tablets used were active, but of different batches, a deliberate departure from fact which was felt to be in the interests of scientific control.

In the second stage each of 99 students (75 men and 24 women) received, in a random order, 3 senna preparation tablets (7·25 mg.) and 3 inert tablets at an interval of a week.

RESULTS

Time of action. This is shown in Table III(*c*) and (*d*). With the senna preparation no student was awakened from sleep by the call to stool: with the inert tablets, 2 men were awakened from sleep.

Consistence of stool. The consistence of the first stool after the senna preparation and inert tablets is shown in Table IV(*c*) and (*d*). With the

senna preparation, in addition to those whose first stool was loose, 13 men and 9 women whose first stool was firm or soft had a second or subsequent loose stool: and with the inert tablets, 4 men whose first stool was firm or soft had a second or subsequent loose stool: thus 50 students had at least one loose stool after the active preparation, and 9 students recorded a similar effect after the inert tablets.

Number of bowel movements. The number of bowel movements experienced in the 23 hours after the senna preparation and inert tablets is shown in Table V(*c*) and (*d*).

TABLE V

NUMBER OF BOWEL MOVEMENTS IN THE 23 HOURS AFTER MEDICATION

	After	Number of subjects with varying number of bowel movements				
		1 movement	2 movements	3 movements	4 movements	More than 4 movements
(*a*)	*Ward trial:* Senna preparation tablets (7·50 mg.)					
	1 tablet	43	6	3	—	—
	2 tablets	31	16	3	2	—
	3 "	17	23	7	5	—
	4 "	12	20	13	6	1
(*b*)	*Student trials:* 3 senna preparation tablets (7·50 mg.)					
	96 men	25	44	18	7	2
	30 women	6	6	10	4	4
	Total 126 students	31	50	28	11	6
(*c*)	3 senna preparation tablets (7·25 mg.)					
	75 men	27	29	12	4	3
	24 women	3	8	7	4	2
	Total 99 students ..	30	37	19	8	5
(*d*)	3 inert tablets	62	28	5	3	1
(*e*)	1 senna preparation tablet (7·25 mg.)	26	12	4	2	—
(*f*)	1 inert tablet	32	12	—	—	—

Bulk and colour of the stools. No change in stool colour was noticed. With the senna tablets, 37 men and 14 women noticed no change in the bulk of the stools: 28 men and 3 women thought it increased, and 10 men and 7 women thought it decreased. With inert tablets, 51 men and 17 women noted no change in the bulk of the stools, 9 men and 2 women thought it was increased, and 15 men and 5 women thought it had decreased.

Side-effects. With the senna preparation, 7 men and 2 women experienced anorexia: 3 men and one woman felt nauseated. With the inert tablets, 8 men experienced anorexia, and 2 men felt nauseated: no woman had anorexia or nausea.

Griping. The results, with the senna preparation and with inert tablets, are set out in Table VI(*c*) and (*d*). Of the 40 men and 17 women who experienced mild or moderate griping after the senna preparation, 21 men and one woman had one or two bowel movements only, neither of which was loose.

In the third stage each of 44 students, 37 men and 7 women, received, in a random order, one senna preparation tablet (7·25 mg.) and one inert tablet at an interval of a week.

RESULTS

Time of action. This is shown in Table III (*e*) and (*f*).

Consistence of stool. This is shown in Table IV(*e*) and (*f*).

Number of bowel movements. This is shown in Table V(*e*) and (*f*).

Side-effects. With the senna preparation, one student felt nauseated and vomited.

Griping. With the senna preparation 7 students had mild griping and one had moderate griping. There was no griping after the inert tablets.

TABLE VI

INCIDENCE OF GRIPING

	After	Griping absent	Mild griping	Moderate griping	Severe griping
(*a*)	*Ward trial:* Senna preparation tablets (7·50 mg.)				
	1 tablet	49	3	—	—
	2 tablets	40	10	2	—
	3 "	38	9	4	1
	4 "	31	15	4	2
(*b*)	*Student trials:* 3 senna preparation tablets (7·50 mg.)				
	96 men	30	51	10	5
	30 women	7	20	3	—
	Total 126 students	37	71	13	5
(*c*)	3 senna preparation tablets (7·25 mg.)				
	75 men	30	28	12	5
	24 women	6	7	10	1
	Total 99 students ..	36	35	22	6
(*d*)	3 inert tablets 99 students ..	85	14	—	—
(*e*)	1 senna preparation tablet (7·25 mg.) 44 students ..	37	7	—	—
(*f*)	1 inert tablet 44 students ..	44	—	—	—

DISCUSSION

To ensure accuracy of dosage in this trial, tablets were used rather than granules. The dosage of 3 tablets used in the majority of the trials with students was chosen to represent the middle of the dose range (2–4 tablets) suggested by the manufacturers. It was thought that a more accurate record of the side-effects would be obtained if the drug was administered to ward patients *in the morning*.

Most subjects (patients and students) did not suffer from "constipation". However, habitual constipation is not in fact a "disease" as the term is ordinarily understood, and there is no evidence that colonic motility is abnormal in persons suffering from constipation, which results from chronic failure to move the bowels when the rectum is loaded.

Comparison of the results obtained with 7·50 mg. and 7·25 mg. tablets with different groups of students shows no significant differences. None of the 269 volunteers uses a laxative regularly, and only 13 (9 men and

4 women) use a laxative occasionally. This presents an interesting contrast to the conclusion published by Reid[3] that 73 of 565 (12·9 per cent) boys and girls of age 15 years took laxatives at least once weekly, figures which may reveal the influence of the parents.

Psychological Factors

Comparison of the results obtained in the controlled trial with students with one standardised senna preparation and one inert tablet shows no significant difference. It appears that one tablet of the senna preparation does not exercise a significant pharmacological effect. Three inert tablets produced a slightly greater incidence of multiple bowel movements and of griping than one inert tablet, but the differences are not significant.

Comparison of 3 senna preparation tablets and 3 inert tablets for "speed of action", multiplicity and looseness of stool, and griping, gives differences which are highly significant.

"Speed of Action" of the Senna Preparation

The mean "speed of action" of 3 tablets of the senna preparation with ward patients was 9·7 hours, but the mean value among 225 students was 12·15 hours (11·75 hours and 12·65 hours in the two groups of students). This difference (2·45 hours) is significant, and can be attributed to the differing times of administration, and to the age-scatter, activity and diets of the two groups of subjects. These and other factors (anxieties, trivial gastrointestinal infections) were no doubt at work to modify the speed of action, but similar factors would obtain in the clinical use of the drug.

Within each group of subjects there is a wide variation in the "speed of action". The results shown in Table III support the conclusion reached in a previous communication[4] that the speed of action of senna quoted by Clark[5] and by Goodman and Gilman[6] as under 6 hours, and after 8–10 hours respectively, is too short, particularly if applied to healthy people.

Stool Consistence

A laxative for routine use should produce a soft rather than a loose stool. In 148 of 225 students who received 3 senna preparation tablets one or more stools were loose. Among 52 ward patients who, on different occasions received doses of 1, 2, 3 and 4 tablets, there was a progressively higher frequency of occurrence of loose stools: the percentage of the group of 52 patients who passed one or more loose stools was respectively 12, 40, 60 and 66 per cent. This suggests that if looseness of bowel is to be avoided with this preparation the initial dose should be one tablet, the number being increased if necessary.

Anorexia and Nausea

The incidence of anorexia and nausea with 3 tablets is about 10 per cent: however, as the incidence after 3 inert tablets is very similar, these symptoms would appear to be psychological in origin.

Griping

The incidence of griping in the ward trial varied from 21 instances after 4 tablets, and 14 cases after 3 tablets (27 per cent), to 3 instances after one tablet.

In the students' trials with 3 tablets 152 students (67·5 per cent) experienced griping, which in 46 cases was moderate or severe.

This difference in the incidence of griping after 3 tablets in ward patients and students is a striking one, and can be attributed in part to the fact that ward patients can move their bowels whenever the call to stool arises, but students going about their normal daily routine must naturally postpone bowel evacuation until a suitable time. It is equally true that in the clinical use of the preparation such hazards of time and place have also to be faced. Griping may of course occur more frequently in students with normal bowel habit than in costive patients who have a higher threshold of bowel discomfort.

Thirty-nine students experienced griping in the absence of other manifestations of overdosage, which are arbitrarily defined as more than 2 bowel movements, or loose bowel movements. Five ward patients experienced griping in the absence of other evidence of overdosage after they had taken doses of 4 tablets and of 3 tablets.

With students and patients who receive one tablet, and with patients who receive 2 tablets, griping is unusual. However, some patients may require 3 tablets as a single dose to produce a laxative effect, and with 3 tablets some subjects experience griping without other evidence of overdosage. Unless griping is invariably the first symptom of overdosage to appear as dosage is progressively increased, the occurrence of griping without other evidence of overdosage conflicts with the view[7] that "the great advantage of prescribing a standardised preparation of constant laxative action is that, once the dose for each patient is decided, there should be no griping since this seems to be a symptom of overdosage".

Sex Differences

There are no significant differences between the results obtained with men and women students.

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