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From the Kustaankartano Home for the Aged, Helsinki, Finland.

Laxative Effect of Sennoside A and Placebo in a Double-blind Cross-over Test

By

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Functional constipation represents a troublesome problem and an administrative and procedural burden for those institutions concerned with geriatric care.

The term functional constipation as used here may be defined as any or all of the following complaints without any known organic cause: Failure of the bowels to move with the customary frequency, sensation of incomplete bowel evacuation, and passage of sparse, hard masses. Functional constipation is a condition which is tolerated fairly well and which often subsides spontaneously within a short time. The treatment must naturally be less dangerous and difficult than the complaint itself.

Because of the nature of functional constipation it is obviously difficult to assess the effect of mild laxatives. Experiences gained in general clinical practice are unreliable because account has to be taken of both spontaneous correction and the placebo effect. Opinions regarding the significance of the last-named factor vary considerably. Clauser *et al.* (1) and Haas *et al.* (2) obtained such poor results with placebo preparations in double-blind tests in functional constipation that in their opinion the double-blind placebo technique need not be used. Zuspan (9), on the other hand, with double-blind treatment of postpartum constipation, achieved the same result with the placebo as with the effective substance.

In the present double-blind cross-over placebo tests we have endeavoured to imitate the conditions under which laxatives are usually employed, with a view to forming an opinion of the rôle of the placebo effect in the treatment of functional constipation at a home for the aged. Moreover, a comparison was made in these tests between the laxative effect of 25 and 50 mg Sennoside A. In preliminary clinical tests we had demonstrated that both 25 and 50 mg Sennoside A have a good effect similar to that of other gen-

erally used laxatives of the same type (3).

Sennosides A and B were isolated from the senna drug in 1941 by Stoll *et al.* (4). Pharmacological investigations (5, 6, 7) produced the impression that Sennoside A was a milder laxative with less risk of spasms and other side-effects than Sennoside B. Clinical tests with pure Sennoside A as a laxative have not been published before to our knowledge. On the other hand, combined preparations containing equal parts of Sennosides A and B have been widely used in clinical practice.

Materials and Methods

The tests were carried out in 9 wards at a municipal home for the aged with a total of 634 beds for healthy old people. Of the 200 patients treated 175 were female. The patients' ages ranged from 62 to 88 years.

The tests made use of a crystalline calcium salt of Sennoside A with an equivalent weight of 449 and a melting point of 225–235°C (decomposition). In paper chromatography and in countercurrent distribution the substance was pure and uniform.

The double-blind cross-over test was made in 2 different series of investigations. First the effect of 50 mg Sennoside A was compared to placebo (50 mg Sennoside A series) and 4 months later 25 mg Sennoside A with placebo (25 mg Sennoside A series).

50 mg Sennoside A series

Tablets with 25 mg Sennoside A and placebo tablets containing inert tablet mass were prepared. All tablets were tasteless and of the same colour, size and shape. Six placebo tablets and six Sennoside, tablets were reserved for each patient. Each series of tablets had its own code and the system was worked out in such a manner that half the patients, selected at random, were first treated with Sennoside, the other half receiving placebo first. The code was opened only after all the patients had been treated and the results assessed.

The routine at the home for the aged was such that the ward sisters administered two tablets of some suitable laxative as a preliminary measure in the treatment of functional constipation. At the beginning of the investigation the nurses were instructed to administer the test tablets in the usual manner and not to tell the patients that a study was in progress. The nurses were not told that one series of the tablets was placebo; instead they were given the impression that two new laxatives were being compared to each other. Furthermore, the nurses were told not to alter their accustomed attitude towards the patients who received the test preparations by subjecting them, for instance, to a more searching inquiry than usual about the results of the treatment.

All those old people who during the test period complained of constipation were given as usual two tablets containing either 50 mg Sennoside A or placebo. If the patient returned on the following day because the first dose had failed to have any effect, another two tablets of the same kind were given. If the condition failed to respond, two more tablets were given on the third day. In those cases in which the third dose failed to be effective within a maximum of 12 hours, the constipation was treated in some other suitable way. If an old person who had been treated in such a manner again came and complained of constipation, the other kind of tablets was given in exactly the same way. The patients were not asked more than usual about the effect of the tablets. The decisive criterion of the effect of the tablets was whether the patient came and asked for further treatment or not. Owing to this arrangement some of the patients, depending on the effect, received only one dose of two tablets, some others two doses and the remainder three doses of the test tablets.

25 mg Sennoside A series

Four months after the termination of the 50 mg Sennoside A series the tests were continued in exactly the same manner with tablets of the same external appearance. This time the Sennoside tablets contained 12.5 mg each. The dose administered was consequently 25 mg Sennoside A at one time.

The nursing staff was told that the previous experiments had revealed a difference in the effects of the two laxatives, but that the tests must be continued in the same manner to make it possible to obtain a better idea of the significance of the difference.

Results

Tables I and II summarize the results of the 25 mg and 50 mg Sennoside A series, respectively. Both series comprised 100 treated patients. In the 25 mg series the treatment could be carried out according to plan in 91 cases and in the 50 mg series in 97 cases. In both Tables, group 1 comprises those patients whose constipation was treated for the first time with Sennoside and for the second time with placebo, while group 2 consists of patients who were treated in the reverse order. The results of treatment have been entered in the Tables with the symbol +, which signifies that constipation was cleared up, or with the symbol 0, which means that the medication failed to have any effect.

Table III was compiled from the results of Tables I and II and shows how many patients had their constipation corrected with 1, 2 and 3 doses of these tablets. It emerges from the combined result of both series that 1 dose of Sennoside A had a better effect than 1 dose of placebo ($P<0.001$). The difference between 3 doses of Sennoside and 3 doses of placebo was also highly significant ($P<0.001$). On the other hand, no difference could be demonstrated between the effects of 25 and 50 mg Sennoside A.

Table I. Survey of the results in the 25 mg Sennoside A series (legend, see text).

Group 1							Group 2						
25 mg Sennoside Day of treatment			Placebo Day of treatment			No. of patients	Placebo Day of treatment			25 mg Sennoside Day of treatment			No. of patients
1st	2nd	3rd	1st	2nd	3rd		1st	2nd	3rd	1st	2nd	3rd	
+			+			21	+			+			15
+			0	+		5	+			0	+		1
+			0	0	+	1	+			0	0	0	1
+			0	0	0	8	0	+		+			4
0	+		+			1	0	+		0	+		3
0	+		0	0	+	1	0	+		0	0	+	1
0	+		0	0	0	1	0	+		0	0	0	2
0	0	+	+			1	0	0	+	+			1
0	0	+	0	+		1	0	0	+	0	+		1
0	0	+	0	0	+	1	0	0	+	0	0	0	1
0	0	+	0	0	0	2	0	0	0	+			7
0	0	0	0	+		1	0	0	0	0	+		1
0	0	0	0	0	+	1	0	0	0	0	0	+	4
0	0	0	0	0	0	1	0	0	0	0	0	0	3
						46							45
+						1	+						1
+			0	0		1	0	+					1
0	+					1	0						1
0			+			1	0	0	0				1
							0	0	0	0	0		1
Total						50	Total						50

Table II. Survey of the results in the 50 mg Sennoside A series (legend, see text).

Group 1							Group 2						
50 mg Sennoside Day of treatment			Placebo Day of treatment			No. of patients	Placebo Day of treatment			50 mg Sennoside Day of treatment			No. of patients
1st	2nd	3rd	1st	2nd	3rd		1st	2nd	3rd	1st	2nd	3rd	
+			+			19	+			+			16
+			0	+		4	+			0	+		6
+			0	0	+	2	+			0	0	0	1
+			0	0	0	10	0	+		+			7
0	+		+			4	0	+		0	0	0	1
0	+		0	+		1	0	0	+	+			4
0	+		0	0	+	1	0	0	+	0	0	0	1
0	+		0	0	0	2	0	0	0	+			9
0	0	+	+			2	0	0	0	0	+		1
0	0	+	0	0	0	2	0	0	0	0	0	0	2
0	0	0	+			1							
0	0	0	0	0	0	1							
						49							48
+			0			1	0	0		0			1
							0	0	0	0			1
Total						50	Total						50

Table III. Laxative effect of Sennoside A and placebo in double-blind cross-over tests.

	Dosage	Constipation cleared up			Dosage	Constipation cleared up		
25 mg Sennoside A series, 91 patients	1 × 25 mg	62	patients	(68%)	1 × placebo	40	patients	(44%)
	2 × ,,	9	,,		2 × ,,	17	,,	
	3 × ,,	10	,,		3 × ,,	7	,,	
		Total 81	,,	(89%)		Total 64	,,	(70%)
50 mg Sennoside A series, 97 patients	1 × 50 mg	71	,,	(73%)	1 × ,,	49	,,	(51%)
	2 × ,,	15	,,		2 × ,,	13	,,	
	3 × ,,	4	,,		3 × ,,	8	,,	
		Total 90	,,	(93%)		Total 70	,,	(72%)
Total results from both series, 188 patients	1 dose Sennoside	133[1]	,,	(71%)	1 dose placebo	89[1]	,,	(47%)
	3 doses Sennoside	171[2]	,,	(91%)	3 doses placebo	134[2]	,,	(71%)

Difference highly significant ($\chi^2 = 20.4$, $P<0.001$)
,, ,, ,, ($\chi^2 = 22.5$, $P<0.001$)

Table IV is composed in such a way that the effect of 1 dose of Sennoside on patients refractory to 1 dose of placebo can be compared with the effect of 1 dose of placebo on patients refractory to 1 dose Sennoside A. In this manner Sen-

Table IV. Laxative effect of 1 dose of Sennoside A and 1 dose placebo on patients refractory to 1 dose placebo and 1 dose Sennoside, respectively, in double-blind cross-over tests.

	No. of patients refractory to 1 dose placebo	Constipation corrected with 1 dose Sennoside	No. of patients refractory to 1 dose Sennoside	Constipation corrected with 1 dose placebo
25 mg Sennoside A series	51	26[2] patients (51 %)	29	4[3] patients (14 %)
50 mg Sennoside A series	48	36[2] ,, (75 %)	26	14[3] ,, (54 %)
Total of both series	99	62[1] ,, (63%)	55	18[1] ,, (30%)

[1] Difference highly significant ($\chi^2 = 13.79$, $P<0.001$)
[2] ,, significant ($\chi^2 = 5.11$, $P<0.05$)
[3] ,, ,, ($\chi^2 = 8.26$, $P<0.01$)

Table V. Laxative effect of 1 dose of Sennoside A and 1 dose placebo on patients refractory to 3 doses placebo and 3 doses Sennoside, respectively, in double-blind cross-over tests.

	No. of patients refractory to 3 doses placebo	Constipation corrected with 1 dose Sennoside	No. of patients refractory to 3 doses Sennoside	Constipation corrected with 1 dose placebo
25 mg Sennoside A series	27	15 patients (56%)	10	1 patient (10%)
50 mg Sennoside A series	27	19 ,, (70%)	7	2 patients (29%)
Total of both series	54	34[1] ,, (63%)	17	3[1] ,, (18%)

[1] Difference significant ($\chi^2 = 8.89$, $P<0.01$)

Table VI. Side-effects.

	Medication	Nausea	Griping	Pain
25 mg Sennoside A series	25 mg Sennoside	2 pat.	1 pat.	0 pat.
	Placebo	3 ,,	0 ,,	2 ,,
50 mg Sennoside A series	50 mg Sennoside	2 ,,	1 ,,	1 ,,
	Placebo	7 ,,	5 ,,	0 ,,

noside A was found on analysis to be more effective than placebo ($P<0.001$). The effect of 50 mg was better than that of 25 mg Sennoside ($P< 0.05$). Moreover, placebo had a significantly better effect in the 50 mg than in the 25 mg series ($P<0.01$).

Table V presents a comparison of the effect of 1 dose of Sennoside on those patients who were refractory to 3 doses of placebo and the effect of 1 dose of placebo on those patients who were refractory to 3 doses of Sennoside. A significantly better effect could be demonstrated with Sennoside ($P< 0.01$). The data in this Table do not warrant the conclusion that there is a difference between the effects of 25 and 50 mg of Sennoside A.

Too potent an effect in the form of diarrhoea was produced in one patient with 25 mg Sennoside and none with placebo in the 25 mg series, whereas in the 50 mg series 12 patients had diarrhoea from 50 mg Sennoside and 3 from placebo. The difference in the incidence of diarrhoea between 25 and 50 mg Sennoside A is significant (Sign test, $P<0.01$).

Table VI shows the incidence of side-effects which the patients ascribed to the medication in the two test series.

Discussion

The results of the present study, seen in Table III, show that approximately half the patients with functional constipation achieved bowel function with 1 dose of 2 placebo tablets. When the treatment was continued for 2—3 days a total of 70 % of the patients could be relieved of their complaint with placebo tablets. The observation that the placebo effect improved when placebo was administered several times consecutively indicates that a time factor and spontaneous correction of the constipation are included in the placebo effect.

In clinical examinations of drugs endeavours are made to eliminate the placebo effect as much as possible (2,8). In order to eliminate the time factor it is therefore reasonable, when studying the effect of laxatives on functional constipation, to ascribe greater significance to the effect of the first administration of a laxative than to that of several repeated ones. If Table III is studied, it will be noted that 1 dose of Sennoside had a better laxative effect than 1 dose of placebo ($P<0.001$). Another method to reduce the interfering influence of the placebo effect is to eliminate from the material so-called placebo reactors, that is to examine the effect of the active substance on those patients who did not respond to placebo. Table IV shows that of 99 patients who were refractory to 1 dose of placebo (non placebo reactors) 63 % had their constipation corrected with Sennoside A. But there were also patients who were refractory to Sennoside and who reacted to placebo. It is apparent from the Table that of 55 such patients 30 % had their constipation corrected with placebo. This naturally reduces the value of the observed Sennoside effect on patients refractory to placebo. Nevertheless, Sennoside had a better effect on patients refractory to placebo than placebo had on patients refractory to Sennoside. The difference was highly significant and argues that Sennoside A had a better laxative effect than placebo.

Table V was constructed in the same

manner as Table IV, on the assumption that patients who failed to react to 3 consecutive doses of placebo are surer non placebo reactors than those who did not react to only 1 dose of placebo. Of 54 patients refractory to 3 doses of placebo and 17 patients refractory to 3 doses of Sennoside, 63 and 18 % reacted to 1 dose of Sennoside and 1 dose of placebo, respectively. Consequently, even when analysed in this manner, Sennoside A had a significantly better effect than placebo.

It is obvious that one cannot completely exclude the placebo effect by the method of selecting in cross-over tests patients refractory to placebo, since in this study there were patients in whom constipation was cleared up with placebo although the laxative failed to produce any effect. One of the most important reasons is probably that two consecutive constipational episodes in one and the same person may be of very different degrees of severity.

The second objective with this double-blind cross-over test was to investigate whether it was possible to distinguish between the effects of two different doses of the same preparation. In the preliminary tests (3) 25 and 50 mg Sennoside A had approximately the same effect. Nor does Table III, which embraces the whole series of patients, reveal any difference between these two dosages. Table IV, which comprises those patients who were refractory to 1 dose of placebo, shows that 50 mg had a better effect than 25 mg Sennoside ($P < 0.05$). No difference between these two dosages can be noted in Table V. The statistical significance of the results in Table IV for a better effect of 50 mg than 25 mg Sennoside is weak, but it is strengthened by the observation that 50 mg Sennoside A had a more potent effect in the form of diarrhoea in 12 patients, whilst 25 mg produced diarrhoea in only 1 patient. The results of the tests may therefore be interpreted to indicate that 50 mg Sennoside has a somewhat more potent laxative effect than 25 mg. Assuming the difference in the effects in Table IV to be real, it can be calculated that a series including approximately twice the number of patients would be necessary to make this difference significant ($P<0.01$).

It is known that the active substance in double-blind placebo tests influences the effect of the placebo preparations (2, 8). It is apparent from Table IV that placebo tablets in the 50 mg Sennoside A series had a significantly ($P<0.01$) better laxative effect than these same placebo tablets in the 25 mg Sennoside A series. In the former series there were, moreover, 3 cases of diarrhoea with placebo, whereas no case of diarrhoea induced by placebo occurred in the latter series. It may furthermore be observed that the incidence of side-effects was highest with placebo in the 50 mg Sennoside A series (Table VI). Possibly these placebo effects in the 50 mg Sennoside A series may be interpreted as support for the view that 50 mg Sennoside A had a better effect than 25 mg.

To summarize, it can be said that there was not a statistically significant difference in the laxative effect of 25 and 50 mg Sennoside in these old persons, who showed a high tendency to placebo reactions. Consequently, the same method cannot be used for a comparison between two different laxatives with a mild effect,

unless a very great number of constipation episodes is studied. It should be possible, by modifying the method so that only the effect of single doses is examined, to carry out such an investigation at a large home for the aged.

This double-blind cross-over test was planned and could be carried out in such a way that it imitated as closely as possible the circumstances under which laxatives are used at the home concerned. The results obtained make it possible to draw certain conclusions about the administration of laxatives in such an institute. From the considerable effect of the placebo, the inference may be drawn that too much laxative is given in the wards and that it should be replaced by some other mode of treatment. On account of shortage of staff it is difficult to introduce a different therapy, unless this is simpler than the administration of tablets. On the other hand, it should be regarded as a therapeutical-technical benefit that functional constipation in the old at a home for the aged reacts so well to placebo as to relieve 50 to 70 % of the patients of their complaint solely by administration of tablets as such. Moreover, if the tablets contain a mild laxative substance without any side-effects, a laxative is obtained which, with a slight contribution in work by the nursing staff, can clear up the majority of cases of functional constipation. It would appear that Sennoside A tablets are well able to meet these requirements for a laxative.

Summary

It was found in a double-blind cross-over test at a home for the aged that 50 % of old persons with functional constipation had their complaint cleared up with 1 dose of placebo tablets. When the treatment was continued for 2—3 days a total of 70 % of the patients could be relieved of their complaint with placebo.

Sennoside A had a better laxative effect than placebo and was more effective in 50 mg than in 25 mg doses. The statistical significance of the difference between the effects of these two doses did not exceed the 95 per cent level but it was strengthened by the circumstance that diarrhoea occurred more frequently after 50 than after 25 mg Sennoside A.

Complaints about side-effects in the shape of nausea, griping and pain in the abdomen were rare and were noted somewhat more frequently after placebo than after Sennoside A.

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