EFFECT OF POLDINE METHOSULPHATE ON GASTRIC SECRETION OF ACID

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Poldine methosulphate ("nacton") is a drug with an atropine-like action which has been described as a selective inhibitor of gastric secretion. Douthwaite and Hunt (1958) have described their experiences with it in patients with duodenal ulcer. As secretory stimulus they gave a test meal which could be expected to produce results which were probably relevant to the response to ordinary food. They showed that in patients taking adequate dosage of the drug without side-effects acid secretion could usually be reduced by half, and they demonstrated also a similar effect in normal subjects (Douthwaite, Hunt, and Macdonald, 1957).

The present paper describes the effect of poldine on the gastric secretion of acid in patients with duodenal ulcer both before and after the injection of large doses of histamine.

Material and Methods

The patients were men between the ages of 19 and 44. All gave clinical histories consistent with the diagnosis of duodenal ulcer, and this was confirmed in every case by radiography. The demonstration of either an ulcer crater or a considerable persistent deformity of the duodenal "cap," or both together, was regarded as confirmatory evidence.

Gastric Secretion Studies

The augmented histamine test (Kay, 1953) was used. It was performed exactly as described more recently (Gillespie, Clark, Kay, and Tankel, 1960). Neoplex duodenal tubes, size 16 French, with eight holes 2 by 4 mm. cut in the terminal 8 cm., were used. Figures were derived for both one hour's "basal" or "spontaneous" acid secretion and the acid output during the half-hour beginning 15 minutes after subcutaneous injection of histamine acid phosphate in a dose of 0.04 mg./kg. body weight (maximal histamine response). Results are expressed in milliequivalents of "free" hydrochloric acid.

A control augmented histamine test was carried out on all patients during the first few days of their treatment in hospital, before they received poldine. The drug was then given in four equal doses spaced evenly throughout the day, the daily dose being gradually increased until side-effects were experienced, these recurring for at least two successive days. The total dose was then reduced by as much as was required to cause these side-effects to disappear; this was usually a reduction of 4 mg. a day. Always the earliest and in most cases the only side-effect was dryness of the mouth on waking in the mornings. In two patients some temporary difficulty in starting to pass urine was experienced, and three patients noticed transient interference with visual accommodation. The total daily dose varied from 24 to 40 mg.; most patients tolerated 32 mg.

Other treatment included a liberal diet and antacids. Barbiturates were not given as a routine, nor was any preparation containing belladonna alkaloids.

Interval Between Poldine and Secretion Test

Series 1.—In 16 patients the last dose of the drug was given 11 hours before the start of the second gastric secretion test. In all these, two to three weeks elapsed

between the performance of the control and the second test; this was the period required to adjust to adequate dosage without side-effects as above.

Series 2.—Six of these patients, and one other, continued to take poldine as out-patients under regular supervision, and were studied a third time after a further 10 weeks. Treatment had then been continued for a period of three months altogether. As in series 1 the last dose of the drug was given 11 hours before the second test.

Series 3.—A further group of 12 patients were treated in exactly the same way as those in series 1, except that the final dose of poldine was given by mouth two and a half hours before start of the second gastric secretion test.

It should be noted that in all these tests one and a half hours elapsed between the start of the collection of spontaneous secretion and the injection of histamine.

Results in Series 1

Table I contains data relating to spontaneous secretion and maximal histamine response in this group, before and after two or three weeks' treatment with poldine.

TABLE I.—Series 1

Spontaneous Secretion (11 hours after Poldine)			Maximal Histamine Response (12½ hours after Poldine)		
mEq Free HCl		% Change	mEq Free HCl		% Change
Before	After		Before	After	
5.76	7.38	+29	20.00	18.95	—5
15.21	8.41	—45	20.63	23.43	+14
0.65	2.56	+294	15.95	18.29	+15
2.06	0.51	—75	20.14	19.35	—3
4.64	2.44	—47	17.86	12.59	—29
0.00	0.57	+100	6.47	7.45	+15
10.34	11.33	+10	24.95	25.80	+3
3.83	0.94	—75	22.90	19.38	—15
10.39	6.16	—41	15.28	18.52	+21
15.70	14.07	—10	25.40	21.50	—15
7.52	7.44	—1	17.81	17.68	—1
4.54	2.59	—43	24.70	22.39	—9
7.06	1.60	—77	27.09	25.35	—6
4.57	2.44	—47	23.28	23.76	+2
1.61	4.76	+195	20.61	17.54	—15
2.14	0.60	—72	14.89	15.83	+6
96.02	73.80		317.90	307.80	

The mean secretion after poldine as a percentage of the mean secretion before poldine is 77% for spontaneous secretion and 97% for maximal histamine response.

After giving poldine the mean "spontaneous" secretion of acid was 77% of that secreted before poldine, but it is apparent from the data of Table I that the variation between subjects makes this small and inconstant reduction of no practical value. This wide variation is likely to occur particularly with spontaneous secretion, as small volumes of gastric juice of variable viscosity make recovery uncertain, in spite of the large bore of the neoplex duodenal tubes used. More consistent results can be arrived at by repeating the test many times, but this was not justifiable with an undeniably uncomfortable and lengthy procedure unless obvious technical failure was encountered.

Under the same conditions there was only a 3% mean reduction in the response to large doses of histamine (Table I). There was much less variation in the volumes collected, as the gastric aspirate after injection of histamine is usually much less viscous.

For reasons discussed below it was not thought worth while to continue these trials over a larger group in the hope of proving the significance of a small effect.

Results in Series 2

Table II contains data from patients undergoing more prolonged treatment (series 2). A small reduction in

secretion of acid was demonstrated in both spontaneous secretion and maximal histamine response (Table II). This group was studied to determine whether treatment continued for a longer period with poldine in full dosage had a more noticeable effect on acid secretion. Such a possibility was suggested by some results in the earlier work already referred to above, when after many weeks' treatment in several cases the effect appeared to persist even for some days after stopping the drug altogether (Douthwaite and Hunt, 1958).

TABLE II.—Series 2 (Continuous Treatment for 3 Months)

Spontaneous Secretion (11 hours after Poldine)			Maximal Histamine Response (12½ hours after Poldine)		
mEq Free HCl		% Change	mEq Free HCl		% Change
Before	After		Before	After	
7.52	15.97	+112	17.81	14.74	-17
4.54	2.28	-50	24.70	23.13	-6
7.06	2.35	-67	27.09	24.29	-10
2.14	2.41	+13	14.89	15.19	+2
4.57	3.02	-34	23.28	23.12	-1
7.49	2.97	-60	23.68	20.61	-13
1.61	0.50	-69	20.61	13.00	-37
34.90	29.50		152.00	134.00	

The mean secretion after poldine as a percentage of the mean secretion before poldine is 85% for spontaneous secretion and 88% for maximal histamine response.

A statistical analysis of the data for spontaneous secretion given in Tables I and II shows that there was a significant (1 in 20 level) reduction after poldine, even 11 hours after the last dose. However, the magnitude of this reduction is not sufficient to be of practical consequence in the treatment of patients. For this reason the drug is usually given in four doses at regular intervals throughout the day.

Results in Series 3

The results in this group of 12 patients taking poldine by mouth two and a half hours before the start of the second test are shown in Table III. With a single exception there was a considerable reduction in spontaneous secretion. After poldine the mean spontaneous secretion of acid was 33% of that secreted before the drug. The maximal histamine response was reduced in all patients, and the mean secretion after poldine was 52% of the mean of the "control" data. Both these results are significant at the 1 in 500 to 1 in 1,000 level.

Discussion

It appears, therefore, that poldine can reduce spontaneous secretion of acid in patients with duodenal ulcer. This effect is such that about three hours after taking

an adequate dose of the drug, acid secretion is reduced by more than half. Eleven hours after the dose the effect is small and inconstant. Since for any hope of therapeutic benefit a considerable reduction of acid is likely to be necessary, a larger series was not examined in an effort to prove such marginal differences, though it seems likely that they exist in many patients even with this lapse of time after taking the drug.

The effect on the maximal histamine response appears to be similar in its time relationships to the ingestion of poldine, and practically no effect was seen 13 hours after oral dosage; but four and a half hours after taking it a reduction by half was seen in most cases.

If series 1 and 3 are compared it will be seen that the duration of stay in hospital and all details of management were the same for both groups. The only difference between the two is in the length of the time interval between the last dose of poldine and the second test. It is reasonable, therefore, to attribute the reduction in acid secretion to the effect of poldine rather than to any other feature in the treatment of these patients.

With the use of the augmented histamine test it has been shown previously that most patients with duodenal ulcer produce about double the normal spontaneous acid secretion (Hunt and Kay, 1954). A reduction by half is therefore likely to be beneficial. Similar results after "physiological" test meals have already been mentioned above (Douthwaite and Hunt, 1958).

That poldine can reduce the acid secretion after maximal histamine stimulation is interesting. Gillespie *et al.* (1960) have shown that in a series of 23 patients with duodenal ulcer who were treated surgically by vagotomy and gastrojejunostomy the maximal histamine response was reduced considerably. If their data are treated in the same way as in this paper the mean reduction is 68%. If the presence of a gastrojejunostomy itself reduces the recovery of acid from the stomach to some extent, then it is reasonable to infer that poldine is highly or even completely effective in blocking the acid-secreting stimulus of the vagus nerves. Its particular usefulness lies in that it seems to exert this effect when taken in oral doses which do not produce side-effects.

Summary

A study of the effectiveness of poldine methosulphate ("nacton") in reducing secretion of acid in the stomachs of patients with duodenal ulcer under certain conditions is described.

The augmented histamine test has been applied before and after taking the drug.

Adequate dosage of poldine without side-effects reduced secretion by approximately one-half about four hours after taking it, and this effect had lessened considerably after 13 hours.

I am grateful to Air Vice-Marshal Sir Aubrey Rumball for supporting this work, and to Professor A. W. Kay and Mr. I. E. Gillespie for much advice and encouragement. I am indebted to Dr. J. N. Hunt for help with the arithmetic. I am grateful to the Director-General of Medical Services, Royal Air Force, for permission to publish.

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TABLE III.—Series 3

Spontaneous Secretion (2½ hours after Poldine)			Maximal Histamine Response (4 hours after Poldine)		
mEq Free HCl		% Change	mEq Free HCl		% Change
Before	After		Before	After	
7.44	2.59	-65	23.40	13.19	-44
2.77	0.00	-100	20.51	1.06	-95
20.75	9.02	-57	34.96	21.95	-37
2.64	0.22	-92	25.78	13.11	-49
1.64	0.00	-100	16.83	9.66	-43
3.88	0.39	-90	29.81	19.32	-35
0.78	0.00	-100	13.55	3.24	-76
10.80	0.00	-100	13.73	4.34	-68
2.50	1.61	-36	36.48	17.18	-53
0.00	0.75	+100	8.29	4.43	-47
5.76	3.81	-34	20.00	16.01	-20
11.09	4.69	-58	11.14	9.68	-13
70.50	23.08		254.50	133.17	

The mean secretion after poldine as a percentage of the mean secretion before poldine is 33% for spontaneous secretion and 52% for maximal histamine response.