therapeutic effect by a reliable experimental screening procedure before a controlled trial is considered. The gastric sampling technique under conditions as close as possible to those in which the drug is used clinically seems to offer such a method. Theoretically, the samples should be withdrawn from the duodenal bulb, but this is difficult technically. A tube placed in this position tends to move back into the stomach or on into the duodenum, and close radiographic control is needed. In practice, gastric sampling is probably adequate, since there is good evidence that gastric acidity parallels acidity in the duodenal bulb (Lopusniak and Berk, 1948; Atkinson and Henley, 1955). The difference, described here and elsewhere (Bingle and Lennard-Jones, 1960), between results obtained when patients take milk–cream drinks and take diet emphasizes the necessity of testing drugs under the actual conditions of use.

Summary

Poldine methosulphate, even in doses large enough to produce severe side-effects, did not reduce the acidity of the gastric contents of patients with duodenal ulcer taking a bland diet.

Gastric acidity was reduced by poldine under special conditions when patients took hourly drinks of milk–cream without other food.

Poldine apparently augmented the effect of a regime of regular antacid by day but did not prolong the effect of a dose of alkali at bedtime.

No therapeutic benefit from poldine in duodenal ulcer was demonstrated in a small controlled trial.

The relevance of these observations to the testing of other antisecretory drugs is discussed.

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CLINICAL EVALUATION OF POLDINE METHOSULPHATE

BY

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Assessment of the therapeutic effectiveness of an anticholinergic drug in duodenal ulcer requires experimental demonstration of substantial inhibition of human gastric secretion, confirmation of antisecretory potency under ordinary dietary conditions, and demonstration of the ability of the drug to abolish or alleviate ulcer symptoms when used on a long-term basis. The large and growing number of drugs available in this category suggests that an antisecretory drug of undoubted benefit in the treatment of duodenal ulcer has not yet been found; indeed, the real clinical value of prolonged therapy of this type has been held in question (*British Medical Journal*, 1955). Poldine methosulphate ("nacton") has been described as a selective inhibitor of gastric secretion and has been reported on favourably by Douthwaite *et al.* (1957) and Douthwaite and Hunt (1958). They studied the effect of poldine on the volume and acid content of gastric juice and observed that acid output could usually be reduced by half without troublesome side-effects appearing.

In the present investigation the clinical value of poldine has been studied by use of the following procedures: (1) inhibition of insulin-stimulated gastric juice; (2) electrometric testing of gastric juice *p*H at two dosage levels during a 24-hour period while on normal diet; and (3) long-term "double-blind" clinical trial on out-patients. All patients had radiologically proved duodenal ulcer.

Materials and Methods

Effect on Insulin-stimulated Gastric Secretion

In six fasting male patients a small-bore stomach tube was passed and the stomach emptied by hand suction. Thereafter the patient was positioned on the left side and continuous supervised mechanical aspiration was applied at a negative pressure of 5 to 10 mm. Hg. Gastric juice aspirated for the first 15 minutes was defined as the control sample. Soluble insulin 15 units intravenously was then given and gastric juice obtained for the next 45 minutes was discarded. Juice collected in the ensuing 15-minute period represented the insulin-stimulated juice, and the free-acid content of this specimen as well as of the control sample was estimated. Several days later the test was repeated, giving poldine 1 mg. intramuscularly immediately before the 15-minute collection of insulin-stimulated juice. Between the tests no treatment had been given other than modification of the diet when necessary. One patient vomited on taking his first meal after completion of the test, and this was attributed to gastric atonicity induced by poldine. A second patient felt nauseated but did not vomit. The gastric juice was titrated against N/10 NaOH using Töpfer's double indicator, and the results were expressed in milliequivalents of hydrochloric acid.

Twenty-four-hour Test of Gastric Juice pH

A Ryle tube was passed into the stomach by the nasal route in seven male patients. The tube remained in

position for 24 hours, and during this period the patient was allowed up if he wished, took "ordinary" or "bland" diet, depending on the severity of symptoms, but received no other treatment. Specimens of gastric juice were aspirated at hourly intervals. On the day after the test poldine 4 mg. was given six-hourly by mouth for five days. On the fifth day the test was repeated. A second group of seven male ulcer patients was submitted to a similar series of tests, but on this occasion the dose of poldine given six-hourly was 8 mg. Several patients in this group, though not in the first group, admitted to dryness of the mouth on direct questioning, but there were no other side-effects. Electrometric determination of gastric juice *p*H was carried out on each specimen. In a few instances the volume of juice was too small for *p*H determination and two adjacent samples were then pooled.

Clinical Trial

A "double-blind" out-patient clinical trial was conducted on 58 male subjects suffering from duodenal ulcer. In all cases a positive *x*-ray diagnosis had previously been made. Of the 58 patients, 31 received poldine tablets containing 2 mg. of the active substance and 27 received a placebo tablet of identical appearance containing lactose. Patients were allocated to poldine or placebo in random fashion by the hospital pharmacist, and neither physician nor patient knew the nature of the individual medication until the end of the trial period. The dosage of tablets was 8 to 12 daily, depending on clinical response and presence of side-effects. A supply of alkali tablets was also given to each patient, to be taken as required for the relief of ulcer symptoms. Out-patient appointments at four-weekly intervals were arranged at which clinical progress was assessed and a new supply of tablets issued. At each visit a clinical grading was made, depending on the symptomatology over the preceding four-week period as recorded by the patient on a card on which he noted, each day, symptoms as they occurred. Grading of severity of ulcer symptoms was made according to the following scale: grade 0, no dyspepsia; grade 1, epigastric discomfort, heartburn; grade 2, slight pain; grade 3, moderate pain; grade 4, severe pain, vomiting.

An exacerbation was regarded as having occurred when there was deterioration by two or more grades. The clinical grade of each patient was compared at the end of the trial with that at the outset; "improvement" was recorded if the grade had fallen by two or more, the patient was "worse" if the grade had risen by two or more, and there was "no change" if the grade varied by no more than one in either direction.

The subjects of the trial had usually been referred because of severe ulcer symptoms requiring out-patient investigation and because recent absence from work had been frequent. Social class distribution was similar in the two groups (Table I). The mean age of the patients was 45.0 years (poldine group) and 44.9 years (placebo group), and the average duration of previous symptoms was 9.5 years (poldine group) and 12.5 years (placebo group). Previous complications had consisted of haemorrhage in 15 (poldine group 8, placebo group 7) and perforation in 6 (poldine group 2, placebo group 4). The average duration of attendance for the 58 patients was 8.8 months.

TABLE I.—*Clinical Trial of Poldine Distribution of Patients by Social Class (Registrar-General Class, 1–6)*

Social Class	2	3	4	5	6
Poldine group	3	19	6	3	0
Placebo ,, ..	2	17	5	2	1

Results

Insulin Test (Table II).—Partial inhibition of insulin-stimulated acid secretion was observed in each case. The mean inhibition was 59%, and the inhibitory effect was statistically significant ($t=4.8$).

TABLE II.—*Inhibitory Effect of Poldine on Acid Response to Insulin Hypoglycaemia. Acid Output in mEq HCl. Poldine Dose 1 mg. Intramuscularly 15-minute Collection Periods*

Case No.	Resting Secretion	Insulin Secretion	Insulin Secretion +Poldine
1	1·6	6·4	3·6
2	2·5	7·6	6·3
3	0·4	5·3	1·2
4	0	2·7	0·8
5	2·8	7·0	5·9
6	0	2·6	0·7

TABLE III.—*Twenty-four Hour Gastric Juice pH Tests with Hourly Aspiration in 7 Duodenal-ulcer Patients During a Control Period, and Following Administration of Poldine Six-hourly by Mouth for 4 Days. Number of Tests in Each pH Range*

*p*H	Control	Poldine 4-mg. Doses	Control	Poldine 8-mg. Doses
1–2	124	74	75	50
2·1–3	26	45	30	53
3·1–4	9	23	19	32
4·1–5	8	6	15	16
>5	2	6	12	9

Gastric Juice pH Tests (Table III).—Since variation in dose response might occur, perhaps due to changing rates of absorption, and because it was desired to ensure that a fully adequate dose of poldine was being given, the test had been performed after four days' administration of the drug in two dosage ranges. In both series of tests there was a significant increase in the number of readings in the higher *p*H range (small dose, $\chi^2=23.4$, $P=0.1$; large dose, $\chi^2=14.9$, $P=1.0$). Even so, it will be noted that only a minority of specimens were in the *p*H range greater than 4, which is desirable if peptic activity is to be reduced to the minimum. With a Wald-type test of statistical significance (Aitchison and Silvey, 1960), the patterns of *p*H change did not differ between the small and large doses, and the latter conferred no apparent advantage.

TABLE IV.—*Results of Clinical Trial*

	Poldine Group	Control Group
Total No. of cases	31	27
Improved	15	8
No change	14	19
Worse	2	0
No. of acute exacerbations	15	11
Total period of observations (months) ..	290	219
Exacerbations per month of observation	0·052	0·052

Clinical Trial (Table IV).—At the end of the trial the number of clinical exacerbations and the degree of clinical change, depending on the severity of symptoms, were compared in the poldine and control groups. The number of exacerbations was identical in the two groups over similar periods of observation, and the pattern of clinical change showed no significant difference between either group ($\chi^2=4.70$, $P=0.10$). No major complication occurred in any patient during the trial. One patient developed symptoms of pyloric stenosis and treatment was discontinued; it was subsequently established that he had been receiving poldine, which is contraindicated

under these circumstances. A few patients reported dryness of the mouth, but there were no other side-effects.

Discussion

There is strong evidence—for example, Woodward and Schapiro (1954)—that elimination of hydrochloric acid from the gastric juice will facilitate healing in duodenal ulcer, regardless of other possible causes. Gastric hypersecretion in this disease is due to parasympathetic overactivity, and it is rational to administer an anticholinergic drug which by inhibiting the vagal mechanism will decrease the output of acid. Additional beneficial effects result from blockade of smooth-muscle innervation, with diminution of gastro-intestinal motility. The antisecretory potency of an anticholinergic drug can best be measured in the duodenal-ulcer patient, in whom acid output is already high, and methods of doing so are numerous and varied. The effect on basal and nocturnal secretion has been studied—for example, Levin *et al.* (1948)—but, since successive tests often show wide variation in the same patient, drug effects are difficult to measure. Physiological conditions are simulated by assessing the suppressive action of the drug on secretion stimulated by a single meal; this test is regarded by Bachrach *et al.* (1954) as fully adequate for evaluation of antisecretory effect, but has the disadvantage that the drug must be given parenterally.

The secretory response to insulin hypoglycaemia is a cholinergic phenomenon mediated vagally, and the suppressive action on it of the anticholinergic drug under trial is a rational method of assessing antisecretory potency; while the conventional two-stage test permits determination of percentage inhibition, it is considered sufficient in preliminary evaluation of a drug of this type to demonstrate that substantial inhibitory potency exists. Ability of the drug to abolish or diminish acid output under histamine stimulation is a stringent test of activity, but the result has limited physiological relevance, and the effect on acid secreted under ordinary clinical conditions is the most pertinent in relation to therapeutic application. The latter can be conveniently determined by 24-hour observations of changes in acidity on normal diet while the drug is being administered.

Suggested criteria of antisecretory potency have consisted of 50 to 75% acid inhibition (Kirsner *et al.*, 1953), achlorhydria persisting for at least 30 minutes (Kirsner and Palmer, 1953), and a rise in gastric juice *p*H to 4.5 or higher (Sun and Shay, 1956). It will be noted that on 24-hour testing these criteria were satisfied by poldine to a limited degree only. Poldine given parenterally during the insulin test caused an adequate degree of inhibition which might even have been improved by adjustment of dosage and modification of the details of the test. Comparison of the drug with atropine is no longer regarded as reliable (Kirsner *et al.*, 1957) and has not been attempted. Although the antisecretory action of poldine has not been observed to be profound, under normal clinical conditions alkalis would be given simultaneously. The antimotility effect of the drug by delaying gastric emptying will permit more complete and prolonged interaction and neutralization of acid by alkalis, and is probably as important as the antisecretory action.

There is often difficulty in determining the optimal dosage of an anticholinergic drug, and it was for this reason that poldine was given at two-dosage levels in the present study. Adjustment of dosage depending on the presence and severity of side-effects is of limited value, while individual variations in pharmacological responsiveness and in rates of absorption create additional hazards in management. The many problems in clinical evaluation of the drug can be overcome by a prolonged double-blind trial which aids in elimination of these and other confusing factors; the necessary criteria for a suitable trial have been defined by Cayer (1956).

In the present study the two groups of cases were closely matched in all important respects. The control group had a longer history of ulcer symptoms, but an impression that the disease was more chronic and intractable in this group was not supported by the almost equal incidence of previous complications in the two series of patients. As decisive indices of long-term clinical effectiveness of the drug, the incidence of exacerbations of symptoms and the final clinical status may be used. Though possibly useful in relieving ulcer pain (Jones and Gummer, 1960), it has been suggested (*British Medical Journal*, 1955) that anticholinergic drugs do not affect the natural history of duodenal ulcer, and the present investigation also indicates that the long-term administration of poldine does not fundamentally alter the course of the disease.

Summary

A clinical evaluation of poldine methosulphate (nacton) in the treatment of duodenal-ulcer patients is described. Measurement of gastric juice *p*H was performed at two-dosage levels before and during poldine therapy, and the degree of inhibition effected by poldine on acid secretion stimulated by insulin hypoglycaemia was also assessed. A significant rise in *p*H or fall in acid output was noted respectively in each case. A double-blind clinical trial over a period of nine months was performed, and it was found that poldine did not significantly reduce the number of acute exacerbations or improve eventual clinical status. Side-effects were either absent or of trivial degree. It is concluded that, in company with other anticholinergic drugs, poldine, by reason of its antisecretory effect, can be usefully employed in the immediate relief of acute ulcer symptoms, but that its administration does not fundamentally alter the course of the disease.

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