conditions because the potential rate of intracellular utilization of glucose exceeds the rate of entry of glucose into the muscle cell (Park *et al.*, 1955). Salicylate, like insulin, increases glucose uptake, expands the xylose space, but does not alter the glucose space. We conclude, therefore, that the action of salicylate in increasing glucose uptake includes acceleration of the rate of entry of glucose into the muscle cell.

The observation that oxygen lack or substances such as cyanide, 2:4-dinitrophenol, and arsenite which inhibit oxidation or uncouple oxidative phosphorylation increase the uptake of glucose by the isolated rat diaphragm (Randle and Smith, 1957) has led to the suggestion that the entry of glucose into the muscle cells of this preparation is normally restrained by an active process (Randle and Smith, 1957). The present observations with salicylate lend support to this idea.

Although both insulin and salicylate increase the glucose uptake of isolated diaphragm their actions on the diaphragm with respect to potassium release and incorporation of amino-acids into protein differ greatly. Salicylate promotes loss of potassium from the muscle and diminishes the incorporation of amino-acids into protein, whereas insulin stimulates amino-acid incorporation and does not promote loss of potassium. Nevertheless both insulin and salicylate may accelerate glucose uptake by interfering with some restraint on glucose entry involving energy-rich phosphate; salicylate, by restricting the oxidative production of energy-rich phosphate; and insulin, not by interfering with the production of energy-rich phosphate, but perhaps by interfering specifically with the availability of energy-rich phosphate to a process concerned with the regulation of glucose entry. Such an action of insulin would neither be incompatible with its ability to stimulate incorporation of amino-acids into protein nor would it interfere with the maintenance of high intracellular potassium.

We attach more significance to the stimulating effect of salicylate on glucose uptake in bicarbonate-buffered medium than to the lack of this effect in a phosphate-buffered medium, because bicarbonate-buffered medium more closely resembles extracellular fluid in ionic composition. Furthermore, phosphate-buffered media are known to be unsuitable for incubation of tissues such as diaphragm which exhibit a high rate of glycolysis (Dixon, 1934), and phosphate-buffered media contain an abnormally high concentration of phosphate, an ion which in high concentration is itself capable of influencing glucose uptake (Villem, Deane, and Hastings, 1949).

Summary

Sodium salicylate, like insulin, increases the uptake of glucose by isolated rat diaphragm, and enables the non-utilizable sugar D-xylose to enter the muscle cells. Neither insulin nor sodium salicylate enables free glucose to accumulate within the cells of isolated diaphragm, presumably because the potential rate of glucose utilization with the cell exceeds the rate of entry of glucose into the cell. The effect of insulin on isolated diaphragm differs from that of salicylate in that salicylate promotes loss of potassium and diminishes incorporation of ^{14}C -labelled amino-acids into the protein, whereas insulin does not promote potassium loss and increases incorporation of labelled amino-acids into protein. The uptake of glucose into the cells of isolated diaphragm appears to be restrained by an active process, dependent upon the oxidative production of energy-rich phosphate. It is suggested that salicylate promotes uptake of glucose by inhibiting the production of energy-rich phosphate and that insulin promotes glucose uptake, more specifically, by limiting the availability of energy-rich phosphate to a process concerned with the regulation of the entry of glucose into the cell.

It is suggested that the antidiabetic action of salicylate results, at least in part, from its effect in increasing the utilization of glucose by muscle.

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EFFECT OF "NACTON" IN PATIENTS WITH DUODENAL ULCER

BY

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One of the mainstays of treatment of patients with duodenal ulcer is the reduction of the acidity of the gastric contents. This is usually attempted by counteracting the acid physico-chemically with antacids. In addition, atropine and drugs with an atropine-like action have long been used to block excitation of the acid-secreting parietal cells. Generally these drugs have two disadvantages in that their action in reducing gastric secretion runs parallel with their side-effects, such as drying of the mouth and interference with visual accommodation, and their effect is capricious even in the hands of experienced workers (Kirsner and Palmer, 1953).

Investigation

The present paper describes the use of "nacton" (1-methyl-2-pyrrolidyl) methyl benzilate methyl methosulphate; I.S. 499), a compound with an atropine-like action of long duration, which has given regular reduction of gastric secretion in patients with duodenal or gastric ulcer at dose levels that did not produce noticeable side-effects. The chemical (Doyle *et al.*, 1958) and pharmacological (Acrod *et al.*, 1957) details and the results of a preliminary study in man (Douthwaite *et al.*, 1957) have been published.

Test-meal Method.—The technique (Hunt, 1954) involves washing out the stomach of fasting patients and giving a 750-ml. test meal containing 50 g. of glucose per litre and a dye which is not absorbed from the stomach. After 30 minutes the gastric contents are recovered, the usual volume being about 300 to 500 ml. when the completeness of the recovery has been checked by washing out the stomach. From the amount and composition of the dye remaining in the gastric contents the volume of the gastric contents which has passed into the duodenum may be assessed, together with the total amounts of acid, chloride, and pepsin secreted. It is then possible to describe the gastric secretion of acid in terms of millilitres of 0.16N hydrochloric acid, the concentration at which it is supposedly produced by the parietal cells (Fisher and Hunt, 1950).

Regulation of Dosage.—The method of regulation of the dosage of nacton varied during the trial, but the aim was to arrive at the maximum not giving side-effects. The first three patients were given the drug initially at eight-hourly intervals. When a change was made to six-hourly doses the incidence of side-effects appeared to be less, presumably because each dose was smaller, and this interval was maintained for all the other patients. The starting dose was usually 8–10 mg. a day, and this was increased at intervals by 4 mg. a day. When the patient became aware of definite side-effects the dosage was always reduced, usually by 4 mg. a day. With less definite side-effects—for example, a little dryness of the mouth in the morning—the dosage was not increased as it would have been had the patient not reported this symptom. These slight effects decreased in a day or two, and the dose was usually raised subsequently. An increased tolerance to the drug developed in some patients, so that the occurrence of a side-effect with a certain dosage during the first few days could not be taken to indicate that side-effects would necessarily reappear when the same dosage was reached 10 days later. A scheme of dosage for clinical use is suggested below.

The Patients.—Twenty-three male patients with a diagnosis of duodenal ulcer and two with gastric ulcer were studied while they were in hospital. In none of them was there any history of recent haemorrhage. Their mean age was 42 years, with a range from 21 to 66, five being over 60. The patients were in no sense specially selected

for the trial, but were representative of a group which does not respond satisfactorily to treatment at home. Four patients were transferred for surgical treatment, three because of pyloric stenosis (7, 8, and 16), and a fourth (3) because of a history of many recurrences. In four other patients the prognosis was thought to be poor, but because they responded well to nacton it seemed advisable to reserve surgical treatment for the future.

To judge from their remarks and their co-operation as out-patients most of the patients found the inconvenience of the test meals balanced by the individual attention they received.

Procedure.—After the co-operation of the patient had been enlisted by explaining to him the purpose of the trial he was given a test meal. He next received placebo tablets at six-hourly intervals for three or four days and his gastric function was retested. From then onwards nacton was given at six-hourly intervals and gastric function was studied from time to time. On some days the test meal was given at 8 a.m. after the drug had been taken at 6 a.m.; on other occasions the morning dose was omitted and the test meal given at 8 a.m. Each patient, except three at New Cross General Hospital, was visited at least once every day by one of us and asked about side-effects and general well-being. The ordinary therapeutic regime as ordered by each physician was continued unchanged throughout the study of the patients except that those receiving belladonna were not given it within six hours of the tests. Some days before the patient was due for discharge nacton was withheld while he was given further test meals. When it became apparent that the drug could be used with safety the last 14 patients in the series were discharged with a supply to take at home. Their progress was checked periodically by tests made two hours after taking the drug.

Results

The account which follows is based on the results of 321 test-meal studies of 25 in-patients, the average period of observation of each in-patient being 30 days. Thirty-six studies of the gastric function of the last 14 of these patients were made during the early months after their discharge.

Patients in Hospital

Fig. 1 is a summary of the reductions of secretion of acid obtained without side-effects following six-hourly doses of

FIG. 1

nacton. The order is that in which the patients presented themselves. For each patient the height of the first column represents the volume of 0.16N HCl secreted in 30 minutes in response to the test meal when he was receiving placebo tablets or no tablets soon after admission. This value served as the control for the subsequent results. The second column represents the volume of the 0.16N HCl secreted in response to the test meal two hours after taking the drug, and the third column that secreted eight to nine hours after taking the drug. Each of these two values is the mean of two or more results obtained shortly before discharge. The dosage of nacton for each patient at this time is shown above his data.

In the first 10 patients with duodenal ulcer the mean gastric secretion of acid two hours after the dose was reduced to 52% of the uninhibited secretion in the control experiments, and eight to nine hours after the dose to 70% of the control. For the second 10 patients with duodenal ulcer the mean response two hours after the dose was 34% of the control, and eight to nine hours after the dose it was 47%. The improvement in the results with the second 10 patients was probably the result of our excessive caution in using the drug in the first 10. From the results for the second 10 patients with duodenal ulcer it can be seen that with six-hourly doses a continuous reduction of gastric secretion of acid to about 50% of the control in response to the test meal can be expected. In patients with marked hypersecretion the inhibition was often greater when expressed as a percentage of the control than in those with lower levels of secretion. Among those with duodenal ulcers the first patient (Case 1) and the last patient (Case 23) responded poorly to the drug. The two patients with gastric ulcer responded satisfactorily.

When the optimal dose was given the drug had little action in causing gastric retention. For the tests two hours after the drug the mean increase in the volume of the gastric contents 30 minutes after taking the meal was 50 ml. in the first 20 patients, an increase of 13%.

The mixed secretions of the cells of the gastric mucosa other than the parietal cells have been supposed to have a statistically constant composition (Fisher and Hunt, 1950). These non-parietal secretions which originate from the whole area of the gastric mucosa are thought to contain bicarbonate ion at a concentration of 0.045N. Presumably these secretions have some protective function, and it is therefore worth recording that the mean output of this component in the first 20 patients with duodenal ulcer was found to be unaltered by full doses of nacton.

Patients Studied as Out-patients after In-patient Treatment

Detailed records of the studies of 14 of the last 15 patients are shown in Fig. 2. The dose of drug and the amounts of acid secreted in response to the test meals by in-patients and out-patients are shown plotted against time for each patient. The duration of in-patient treatment is shown in days; that for out-patients is given in weeks. So far nacton seems about as effective in reducing the secretion of acid in out-patients as it is for patients in hospital.

Relation Between Dose of Nacton and Inhibition of Gastric Secretion.—In the preliminary work (Douthwaite *et al.*, 1957) in connexion with nacton it was possible to establish a more or less regular relationship between the size of a single dose of the drug and the inhibition of the gastric secretion of acid. In the present studies with continuous dosage the relationship was not so clear, possibly because the effects of the drug were occasionally slow to develop. The record for Case 20 illustrates this: the drug had little action on gastric secretion during the first six days of treatment, although apparently it was absorbed, since there were urinary side-effects. Later, when dosage with the drug was restarted, a similar or slightly lower dose caused a progressive fall in the output of acid. In nine patients out of the last 14 the gastric secretion of acid after stopping treatment in hospital was found to be less than it was in the control studies before treatment.

Effect on Symptoms.—Doses of nacton which were effective in lowering gastric secretion did not immediately abolish pain, so that the drug presumably did not act as an anaesthetic. This is of some importance in that an increase in the size of the ulcer presumably would give rise to pain (Raftsky *et al.*, 1954).

Side-effects

The most frequent side-effect was dryness of the mouth. In a few patients there was difficulty in beginning to pass urine and in maintaining a vigorous stream. In Case 1 there was retention with a palpable bladder. However, when one dose of the drug was omitted this sign was abolished, and with a subsequent reduction in dosage it did not recur. Difficulty in micturition was usually accompanied by dryness of the mouth, which the patient counteracted by drinking. This further augmented the filling of the bladder and increased the discomfort. It was found best to allay the dryness of the mouth temporarily with mouth-washes.

The drug was given to three patients with pyloric stenosis (7, 8, 16), subsequently confirmed at operation, without producing any marked slowing in the gastric emptying of the test meal and without there being any ordinary food remaining in the stomach in the morning. In patient 5, who was found to have an enlarged prostate on rectal examination, the careful administration of nacton produced 30% inhibition of gastric secretion of acid without any urinary symptoms. With our present experience higher doses could have been tried.

Patients in hospital have reported interference with visual accommodation coming on after reading for some minutes. A raised heart rate has been the reason for reducing the dosage for only one in-patient (19), but in out-patients tachycardia has been noted in patients 12, 19, 24, and 17. It seems likely from the remarks of Nos. 12 and 19, who were able to record their pulse rates at home, that the maximal rate was reached about two hours after the morning dose but that similar rates were not reached after later doses. Since the out-patients are seen precisely at this time of day for their test meals it is possible that our routine has made this side-effect more likely than it will be in actual practice. Certainly the rates observed by Nos. 12 and 19 at home were 20–30 beats a minute less than those observed by us on the days of the tests. Should tachycardia occur it might be avoided by giving the dose after breakfast and after the midday meal, with the idea of slowing absorption of nacton.

Constipation when it occurred cleared up without reduction of the dosage of the drug in these 25 patients. It seems possible that the small amounts of magnesium which were present in the majority of the antacids which the patients were taking, together with the liquid paraffin often supplied in hospital, may have minimized the occurrence of this side-effect.

It must be emphasized that side-effects in hospital were for the most part deliberately produced, and were subsequently abolished by a small decrease in dosage. We observed in two patients that a dosage of the drug which produced no side-effects during continuous administration gave side-effects when it was restarted after an interruption of seven days. The reductions of gastric secretion recorded in Fig. 1 were observed in the absence of side-effects which we regard as an indication of overdosage.

Discussion

In 23 patients with duodenal ulceration under treatment in hospital it has been possible to reduce the gastric secretion of acid in response to test meals during the period between two hours and eight hours after giving doses of nacton carefully adjusted not to produce side-effects. For the second 10 patients with duodenal ulcer the secretion of acid was reduced to about half of the control value. Since in groups of patients with duodenal ulcer the gastric secretion of acid in response to test meals is about doubled (Hunt,

FIG. 2

1957) as compared with that in healthy subjects, the drug may be said to correct this abnormality.

These results are probably relevant to the response to ordinary food, since the test meal used in this work is thought to stimulate gastric secretion by virtue of its volume (Macdonald and Spurrell, 1953; Hunt and Macdonald, 1954), a property necessarily common to all meals. Further work is required to decide whether nacton inhibits secretion in response to other modes of stimulation.

In view of the numbers of drugs which have been tried it is not surprising that another drug with atropine-like action has been found which will depress the gastric secretion of acid, but as compared with atropine the degree of specificity and the duration of its action are interesting. In our experience the maximal inhibition of gastric secretion was often obtained with doses of nacton which produced no noticeable side-effects. The finding that the fall in the gastric secretory response to test meals persisted for up to three days after the drug was discontinued seems worth further study.

Clinical Use of Nacton.—The study reported here was made under conditions remote from those under which inhibitors of gastric secretion can ordinarily be used, and it is clearly undesirable that the dose of nacton should have to be regulated by measurements of the gastric secretory response. However, our finding that full inhibition of gastric secretion of acid was often achieved by doses which produced no side-effects provides a means of regulating the dose by increasing it at four-day intervals from 2 mg. six-hourly to 3, 4, and 5 mg. six-hourly, and so on until side-effects are observed. The reduction of the dosage by one step abolished side-effects and usually gave satisfactory control of the secretion of acid. We observed in two patients that a dose of the drug adjusted to no side-effects on continuous use gave side-effects if it was restarted after seven days' omission. Where a short period of tachycardia, of urinary retention, of constipation, or of pupillary dilatation must be avoided the drug is contraindicated.

Summary

Twenty-three patients with duodenal ulcer and two with gastric ulcer were given six-hourly doses of nacton ((1-methyl-2-pyrrolidyl) methyl benzilate methyl methosulphate; I.S. 499), a drug with an atropine-like action of long duration, while they were in hospital. For each patient the final dose chosen was that which produced no side-effects. The changes in gastric secretion of acid were studied with test meals. Fourteen of these patients were treated as out-patients and studied with further test meals.

In the second 10 patients the gastric secretion of acid was reduced by half during a period between two hours and eight to nine hours after taking the drug.

Effective dosages of nacton produced little change in the rate of gastric emptying and no change in the mean output of gastric non-parietal secretions.

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ALOPECIA FOLLOWING TREATMENT WITH DEXTRAN SULPHATE AND OTHER ANTICOAGULANT DRUGS

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Dextran sulphate has a pharmacological action similar to that of heparin (Ricketts, 1952; Walton, 1952). It differs from heparin in its more prolonged anticoagulant and greater cumulative effects (Ricketts *et al.*, 1953; Donzelot *et al.*, 1955; Jeavons *et al.*, 1956; Cohen and Tudhope, 1956). The commonest toxic effect of dextran sulphate is transient alopecia, which has been described in about 10% of cases (Donzelot *et al.*, 1955; Jeavons *et al.*, 1956), but the frequency of this complication has probably been underestimated, because it may not appear until several weeks after treatment has been stopped. Hjort and Stormorken (1957) have described 10 cases treated with high dosage of dextran sulphate in which loss of hair developed 8 to 10 weeks later. We previously reported that 3 out of 11 patients treated with dextran sulphate developed loss of hair (Cohen and Tudhope, 1956); when these patients were followed up for a longer period the incidence of alopecia was found to be much greater, and we now report the occurrence of this and other toxic effects in 27 patients treated with dextran sulphate. The incidence of alopecia was also studied in 60 patients treated with heparin and an anticoagulant of coumarin type.

Clinical Data

Three groups of patients were studied: those in the first group received dextran sulphate alone; in the second group dextran sulphate was given with a coumarin drug; and in the third group heparin and a coumarin drug were used.

Group 1: Dextran sulphate (total dose 90,000 or more units).—Dextran sulphate was given by repeated intravenous injection to 15 patients. The individual dose was kept constant at 5,000 units, and the frequency of injection was varied in order to maintain the clotting-time at more than twice the value before treatment. It was found that, whereas injections were required eight-hourly during the first 24 hours, 12-hourly dosage was sufficient after 24 to 48 hours, and after 5 to 11 days of continuous treatment one injection every 24 hours was sufficient (Cohen and Tudhope, 1956).

Group 2: Dextran sulphate (total dose less than 40,000 units) with an oral anticoagulant.—Dextran sulphate was given concurrently with ethylbiscoumacetate or phenindione to 12 patients, 5,000 units being injected intravenously eight-hourly for 24 to 48 hours. Treatment was then continued with the oral anticoagulant, the dose of which was regulated to maintain the one-stage prothrombin time two to two and a half times the normal control. The average daily dose of ethylbiscoumacetate was 442 mg.; of phenindione it was 100 mg.

Group 3: Heparin and oral anticoagulant.—Heparin was given with an oral anticoagulant to 60 patients, in whom acute myocardial infarction was diagnosed in 46, pulmonary embolism in 12, and thrombosis of the leg veins in two. In