Treatment of Chronic Gastric Ulcer with Carbenoxolone and Gefarnate: A Comparative Trial

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Summary
In 68 patients with chronic gastric ulcer treated in an outpatient clinical trial with either carbenoxolone or gefarnate ulcer healing was consistently greater during carbenoxolone treatment, even though the dose of gefarnate was ultimately increased to four times that recommended. One-third of the patients receiving carbenoxolone gained weight rapidly and unexpectedly, and were given diuretic treatment, compared with two of the 55 patients receiving gefarnate, neither of whom developed clinical oedema.

Introduction
Controlled trials have repeatedly shown that carbenoxolone sodium promotes the healing of gastric ulcers and that side effects of fluid retention and electrolyte disturbance occur often enough to limit the freedom with which the drug can be used (Doll et al., 1968; Turpie and Thomson, 1965). Another compound, gefarnate (geranyl farnesylacetate), is claimed to be free of such side effects and, from uncontrolled studies and two limited controlled trials, to promote gastric ulcer healing (da Grada et al., 1967; Giovaneli, 1963; Nemark et al., 1970). We have therefore compared directly the clinical efficacy of gefarnate with that of carbenoxolone sodium.

Gefarnate is a terpene which contains a number of isoprene units, the basic fragments, from which pentacyclic ring structures like steroids can be synthesized and with which the triterpenoid, carbenoxolone, bears some structural resemblances. Nevertheless, carbenoxolone has a relatively fixed sterol form whereas gefarnate is conformationally mobile, and structural resemblances may be more apparent than real (see formulae).

Patients and Method
Patients under the age of 70 years with gastric ulcers thought suitable for outpatient treatment were referred to a special clinic and barium-meal examination was carried out on the same day. They were then included in the trial unless (1) the ulcer had healed, the area was difficult to measure, or was less than 10 mm² when measured in maximum profile; (2) a second gastric ulcer was present; or (3) there were clinical reasons such as hypertension, heart disease, or suspicion of malignancy which made inclusion in the trial undesirable. The number of patients referred was 128, and 55 of them were excluded for various reasons (table I). Patients in the trial were advised to continue at work if possible, to take a normal diet with frequent meals, to limit alcohol intake, and to stop smoking. Antacids were given when needed for the relief of pain.

Treatments were allocated at random by reference to a prearranged treatment schedule held by the hospital pharmacist. Carbenoxolone was given throughout in a dose of 100 mg three times daily, while gefarnate was prescribed in a dose of 50 mg four times daily for the first group of patients and in doses of 100 and 200 mg four times daily for succeeding patient groups.

![Structures of carbenoxolone and gefarnate.]

**TABLE I—Reasons for Exclusion from Trial of 55 Patients**

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer too small or healed</td>
<td>38</td>
</tr>
<tr>
<td>Duodenal ulcer only present</td>
<td>6</td>
</tr>
<tr>
<td>Gastric ulcer difficult to measure</td>
<td>4</td>
</tr>
<tr>
<td>Coincident hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous reasons</td>
<td>5</td>
</tr>
</tbody>
</table>

All treatments were given for a period of four weeks and at each weekly visit clinical details, including weight, blood pressure, and the presence of side effects, were recorded. Serum electrolyte levels were measured at the start and the end of the trial and a further barium-meal examination was carried out on the last day. Almost all the radiological examinations were done by a single observer (D.R.K.) who did not know which of the treatments the patients were receiving. The area of the ulcer niche was measured in maximum profile with a millimetre-squared grid, and the effect of treatment was assessed in terms of the percentage change in ulcer size.

Results
Five of the 73 patients admitted to the trial failed to complete the full treatment period. Two were receiving carbenoxolone and three gefarnate, and all except one were symptom-free when last seen. The comparability of the 68 patients completing the trial is analysed in table II. Patients receiving gefarnate tended to have shorter symptomatic histories and slightly larger ulcers at initial examination than did those given carbenoxolone, but
no correlation could be found between either of these factors and the clinical responses to treatment.

The results of treatment are shown in tables III and IV. Ulcer healing was clearly more complete in the first 11 patients who received carbenoxolone than in the 11 receiving gefarnate 200 mg daily (mean reduction in ulcer size 75-6 and 37-0% respectively). The apparently low healing effect of gefarnate, however, was partly due to one ulcer, which more than doubled in size during treatment. In view of this bias, which could have concealed a considerable true overall healing effect, and the absence of side effects during gefarnate treatment the trial was continued with a doubled dose of the drug at 400 mg daily. When a further group of 23 patients had completed treatment average healing was much improved in the gefarnate-treated patients, though remaining slightly but not statistically significantly inferior to the control carbenoxolone-treated group. Again, no side effects were observed during gefarnate treatment. A third group of patients was therefore given carbenoxolone as before or 800 mg daily of gefarnate, but healing in this gefarnate-treated group tended to be less complete than with 400 mg daily (average reduction in ulcer size 47-6 and 69-3% respectively). Though there were no significant differences between any of the three treatment pairs carbenoxolone treatment was clearly superior when taken overall (table IV), and this difference from gefarnate was highly significant (P < 0-01).

Side effects

Details of side effects are shown in table V. Two patients receiving the highest dose of gefarnate gained weight rapidly and unexpectedly. They were the 12 patients given concurrent thiazide diuretic treatment with potassium supplements, though at no time did they develop clinical oedema. In contrast, 12 patients on carbenoxolone were also given diuretic treatment and seven of them had pitting ankle oedema. All responded satisfactorily to treatment despite concurrent carbenoxolone administration.

Blood pressure changes were somewhat greater in carbenoxolone-treated than gefarnate-treated patients, but all variations were small. There were no consistent changes in serum electrolyte concentrations in patients taking gefarnate. Serum sodium levels tended to rise and serum potassium levels to fall in patients receiving carbenoxolone without diuretics, though the changes were small except in one patient who developed pronounced hypokalaemia (serum level 2:2 mEq/l.) and muscular weakness during diuretic treatment.

Discussion

These results indicate that carbenoxolone sodium is more effective in promoting ulcer healing than gefarnate even when the latter drug is prescribed in four times the recommended therapeutic dose. No similar direct comparisons between the two drugs have been made, but one small controlled comparison suggested that gefarnate is clearly superior to a placebo (Newcomb et al., 1970). We have preferred to use the yardstick of a well-proved medical treatment, carbenoxolone, against which to measure the value of gefarnate, and our results do not necessarily imply that gefarnate is valueless.

In our study ulcers healed on average by 80-6% and 51-7% respectively when taken overall in patients receiving carbenoxolone and gefarnate, a ratio of 1:0-64. By contrast, in two previous controlled comparisons between carbenoxolone and placebo treatments, conducted in an almost identical manner to our own, healing with carbenoxolone and placebo averaged 72% and 35% and 78% and 39% (Doll et al., 1962, 1965), yielding ratios of 1:0-49 and 1:0-50 respectively. The lower ratio of 1:0-64 obtained by us with gefarnate and carbenoxolone therefore suggests that gefarnate may have some, if weaker, healing properties than carbenoxolone.

Interpretation of the healing responses to the three different dose levels of gefarnate is difficult. The apparent increase in effectiveness with a rise from 200 to 400 mg daily was due in part to the effect of a single ulcer in the low dose group which increased markedly in size during treatment. Exclusion of this figure from consideration would raise overall healing in the low dose group from 37 to 62%—nearly the same as the figures obtained with the middle dose of gefarnate. The absence of any incremental response to a further doubling of gefarnate dose argues that any effect of the drug is probably maximal at 400 mg daily, and this should probably be used in any future clinical studies. If the apparent lack of side effects with gefarnate is taken into account possibly the drug may have a limited place in the treatment of gastric ulcers in the elderly or in those with cardiorespiratory disease who are particularly prone to fluid retention.
Reduction of Absorption of Paracetamol by Activated Charcoal and Cholestyramine: A Possible Therapeutic Measure

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Summary
The absorption of an oral 2-g dose of paracetamol was markedly reduced by the simultaneous oral administration of either activated charcoal or cholestyramine but was only slightly reduced when the adsorbents were given 80 minutes after the paracetamol. Since the absorption of a larger dose of the drug will probably be slow, the administration of adsorbents may be of value even when delayed several hours.

Introduction
A possible therapeutic measure to reduce liver damage after an overdose of paracetamol (Proudfoot and Wright, 1970; Clark et al., 1973) would be the slowing of the absorption of the drug from the gastrointestinal tract. Oral administration of activated charcoal decreases the absorption of aspirin (Levy and Tsuchiya, 1972), while the anion-exchange resin cholestyramine also decreases the intestinal absorption of some drugs (Gallo et al., 1965). Our in vitro experiments indicated that paracetamol was firmly bound by both of these adsorbents, and therefore decided to investigate their efficacy in man in slowing the absorption of paracetamol from the gastrointestinal tract.

The presumptive absorption of a therapeutic dose of paracetamol in normal subjects was first studied by measuring plasma levels of the drug after an oral dose and then noting the effect on these of activated charcoal and cholestyramine given by mouth at two different times. We also measured the presumptive rate of absorption in patients who had previously taken an overdose of paracetamol to determine whether differences in absorption were responsible for the variable degrees of hepatic damage observed in these patients.

Methods
Normal subjects and patients were fasted overnight. Venous blood samples were taken 5, 10, 20, 40, 60, and 120 minutes after ingestion of 2 g paracetamol with 200 ml water. The plasma concentration of paracetamol was determined as follows: 0.5 ml plasma was added to stoppered test-tubes containing 300 mg sodium chloride, 10 ml of diethyl ether (Analar) was added, and the tubes were shaken by hand for 30 seconds. After centrifugation at a maximum of 1,300 g for 10 minutes the upper phase was removed and the absorbance at 250 nm determined. Recovery of standard amounts of paracetamol from plasma by ether extraction was greater than 90%, and after calibration there was no significant difference between values obtained with five paired samples measured both by this spectroscopic method and by gas-liquid chromatography. The plasma paracetamol concentrations were plotted against time, and by using the trapezoidal rule the area under the curves was calculated as an estimate of the amount absorbed. Student's t test was used for assessment of statistical significance.

Results
The mean plasma absorption curve of paracetamol in 14 normal subjects is shown in fig. 1. The drug was rapidly absorbed, with peak plasma levels at 40 to 60 minutes. The concentrations at that time ranged from 18 to 87 µg/ml. The absorption of paracetamol was then restudied in these subjects under the same conditions but for the addition of activated charcoal or cholestyramine. Seven subjects ingested 10 g charcoal given as a suspension in methylcellulose (20 g/100 ml) immediately after the paracetamol. Mean plasma paracetamol levels were considerably lower (fig. 1), with a 63 ± 7% (mean ± S.E. of mean; range 32-87%) reduction in absorption measured as the