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Serum carbenoxolone in patients with gastric and duodenal ulcer

Absorption, efficacy and side-effects

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SUMMARY The absorption of carbenoxolone sodium has been studied in 15 patients with gastric ulcer and eight patients with duodenal ulcer treated for four weeks. Blood levels of carbenoxolone showed a log distribution, varied markedly between patients, and were significantly higher after Biogastrone tablets (300 mg/day) than after Duogastrone capsules (200 mg/day). Serum carbenoxolone levels were similar in patients taking Biogastrone tablets before or after meals, and in patients taking Biogastrone tablets or Duogastrone capsules with or without antacids following chronic administration. Serum carbenoxolone levels were similar in patients whose gastric ulcers had or had not healed after four weeks' treatment. Serum carbenoxolone was significantly higher in patients who developed oedema, and was significantly correlated with age and with fall in plasma potassium. Carbenoxolone may exert its metabolic effects systemically, but its ulcer-healing effects topically; additional studies are needed to test this hypothesis.

The specific gas liquid chromatographic method of Rhodes and Wright (1974) for the measurement of serum carbenoxolone has made possible investigations of the absorption of this drug. In a preliminary communication (Baron *et al.*, 1975) we reported that blood levels varied markedly between patients and were higher in patients with gastric ulcer after Biogastrone tablets than in patients with duodenal ulcer after Duogastrone capsules. We have now extended these observations to full four week courses of treatment, and have correlated the serum carbenoxolone of the patients with their clinical, endoscopic, and metabolic responses.

Methods

PATIENTS

Fifteen patients with gastric ulcer, and eight with duodenal ulcer disease, were prescribed carbenoxolone sodium, and gave informed consent to the taking of blood samples. The diagnosis was established by barium meal in every patient, by gastroscopy in each patient with gastric ulcer, and by duodenoscopy in five of the eight with duodenal ulcer disease.

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TREATMENT

Gastric ulcer

The 15 patients received on day 1 a single dose of carbenoxolone sodium 100 mg as Biogastrone tablets, and for the next seven days while in hospital 100 mg three times a day. This dose was continued for the next three weeks in patients 1-9, but halved to 50 mg three times a day (the manufacturers' recommended dose) in patients 10-15 (Table 1). Patients 1-8 were allocated randomly into four pairs receiving carbenoxolone half an hour before or after food, with or without antacid (10 ml magnesium trisilicate mixture B.P.C.). One patient (ES) in error received 100 mg before meals on day 1 and after meals subsequently. Patients 9-15 received carbenoxolone after meals without antacids.

Duodenal ulcer

Eight patients with duodenal ulcer received on day 1 a single dose of carbenoxolone sodium 50 mg as one

Duogastrone positioned-release capsule, 30-45 minutes before breakfast. On each of the next 27 days they took one 50 mg capsule four times daily before meals. The patients were divided randomly so that four patients took the drug with, and four without antacid (see Table 2).

Blood sampling

Venous blood samples were taken on days 1 and 2 at 0, 1, 2, 4, 6, and 8-12 hours after the first dose of drug. On days 3-8, with the patient fasting, blood was withdrawn at about 9 a.m. On days 14, 21, and 28 blood was taken in the afternoon at the clinic. Blood was taken from patients 10-15 with gastric ulcer on days 7, 14, 21, and 28 only. Plasma urea and electrolytes were determined and an aliquot of serum was stored at −20°C for subsequent analysis of carbenoxolone by the gas liquid chromatographic method of Rhodes and Wright (1974). The specimens were analysed without prior knowledge of diagnosis or treatment.

Observations

The patients were seen weekly for assessment of symptoms, side-effects, weight, blood pressure, and blood tests. Endoscopy was repeated at the end of the treatment (unless the patient refused).

Calculations

Concentrations of serum carbenoxolone were not normally distributed, but could be normalised by logarithmic transformation. The significances of difference of means and correlation coefficients have therefore been presented after log normalisation or by the non-parametric Mann-Whitney U test and Spearman's rank correlation.

Results

ABSORPTION AND FOOD (Fig. 1) (Table 1)

Patients with gastric ulcer receiving carbenoxolone after food showed significantly lower blood levels in the first few hours than those taking the drug before food, but for the rest of the four weeks there were no marked differences.

ABSORPTION AND ANTACIDS (Figs. 2, 3) (Tables 1, 2)

In patients receiving Biogastrone tablets there were no marked differences in serum carbenoxolone, either in the initial absorption phase or in the following weeks, between those receiving the drug with and without antacid (Fig. 2). In patients receiving Duogastrone capsules the mean serum carbenoxolone in those taking antacids was markedly higher in the first two days than in those not taking antacid (Table 2, Fig. 3). In the last three weeks of the study one patient receiving Duogastrone alone showed blood levels which were greater than 100 μg/ml. However, all the other patients, whether receiving Duogastrone alone or with antacid, showed similar blood levels ranging from 5 to 40 μg/ml, so

Table 1 *Serum carbenoxolone levels in patients with gastric ulcer given carbenoxolone sodium as Biogastrone tablets*

	Initials															
	HC	*EG*	*JW*	*AS*	*JS*	*JM*	*VF*	*LP*	*ES*	*CF*	*PB*	*LP*	*HR*	*DH*	*PM*
Sex	M	F	M	M	M	M	F	M	F	M	M	M	F	F	M
Age (yr)	53	56	63	59	73	42	51	57	69	71	65	74	72	75	66
Weight (kg)	62	75	81	83	55	82	45	68	59	50	63	54	52	62	57
	Biogastrone														
	100 mg on day 1, 100 mg three times a day on days 2-28									*100 mg on day 1, 100 mg three times a day on days 2-7, 50 mg three times a day on days 8-28*					
	After meals with antacid		*After meals without antacid*		*Before meals with antacid*		*Before meals without antacid*		*After meals without antacid*	*After meals without antacids*					
Serum carbenoxolone (μg/ml)															
Mean days 7-28	48	219	110	34	ND	38	144	46	42	76	72	74	67	38	138
Highest	62	320	147	45	ND	54	213	59	57	90	85	94	70	55	158
△Weight (kg)	+10·5	+1·4	+5·7	−0·1	−0·9	+2·0	+0·9	+3·7	+4·4	+2·2	+1·2	ND	ND	ND	ND
Oedema	+	0	+	0	0	0	+	0	+	+	+	+	0	0	0
△BP (mmHg)	+50/20	+80/10	+60/10	+70/10	−10/0	+30/0	+70/30	+30/5	+60/30	+30/10	+40/10	+10/0	ND	ND	+20/+10
△K (mmol/l)	−0·1	−1·6	−0·8	−1·7	−0·6	−0·5	−1·6	0	−0·6	−0·8	−1·4	−1·1	−1·2	−0·5	−1·9
Symptoms	0	0	0	0	ND	0	Less	0	0	0	0	0	0	0	0
Endoscopy	Healed	Healed	Healed	Healed	ND	Healed	ND	Healing	Healing	Healed	ND	Healed	Healed	Healed	Unhealed

Patients are represented by initials. (ND = not determined; + = present; 0 = absent.)

Table 2 *Serum carbenoxolone levels in patients with duodenal ulcer given 50 mg carbenoxolone sodium (Duogastrone) on day 1 and 50 mg four times daily on subsequent days*

	Initials							
	HR	*FM*	*MM*	*MK*	*LH*	*ES*	*GL*	*RB*
Sex	F	M	F	F	F	F	M	M
Age (yr)	61	39	37	23	19	66	34	32
Weight (kg)	80	82	46	58	54	65	69	73
	Duogastrone							
	With antacid				*Without antacid*			
Serum carbenoxolone (μg/ml)								
Mean days 7-28	ND	7	23	23	23	103	8	33
Highest	ND	10	43	40	35	133	12	38
Δ Weight (kg)	+0·1	0·0	−1·8	−0·9	−0·5	+4·2	+4·5	ND
Oedema	0	0	0	0	0	+	0	0
ΔBP (mmHg)	+10/0	+70/70	+40/15	0/0	−20/0	+10/10	0/0	ND
ΔK (mmol/l)	ND	−0·4	+0·2	−0·3	+0·3	−0·9	−0·0	−0·2
Symptoms	0	0	+	+	0	0	0	0
Endoscopy	ND	ND	ND	Healed	ND	Healed	Unhealed	Healed

Patients are represented by initials. (ND = not determined; + = present; 0 = absent.)

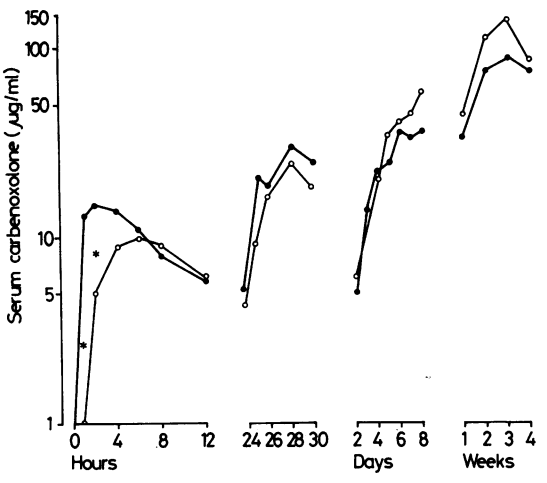

Fig. 1 *Gastric ulcer. Comparison of mean serum levels of carbenoxolone when Biogastrone tablets were administered before food (●) in five patients and after food in four patients (○). In this and subsequent graphs an asterisk denotes a significant difference (P < 0·05) by Mann-Whitney u test.*

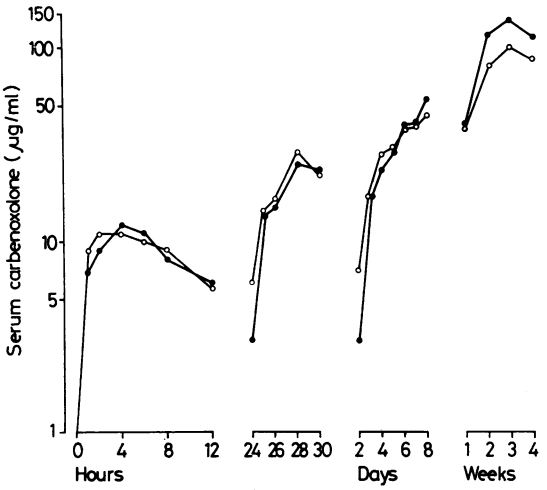

Fig. 2 *Gastric ulcer. Comparison of the mean serum levels of carbenoxolone when Biogastrone tablets were administered with antacid (●) in four patients and without antacid (○) in five patients.*

that, as with Biogastrone tablets, antacid administration did not affect the steady state blood level of carbenoxolone during chronic administration.

BIOGASTRONE/DUOGASTRONE

Blood levels of carbenoxolone were lower in patients receiving Duogastrone capsules (200 mg/day) than in those taking Biogastrone tablets (300 mg/day). These differences were most marked and statistically significant in the first two days and the last three weeks.

AGE

In the 15 patients with gastric ulcer treated with Biogastrone tablets 300 mg daily for the first week there was a significant correlation between serum carbenoxolone and age (Fig. 4). Five out of six of the patients under 60 years had serum levels less than 50 μg/ml (Table 1), whereas seven out of nine of the patients over 60 years of age had serum levels more than 50 μg/ml (Tables 1 and 2).

DOSAGE OF BIOGASTRONE (Table 1)

Patients with gastric ulcer receiving Biogastrone

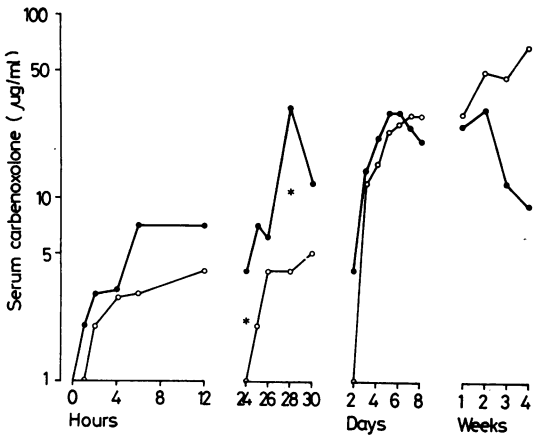

Fig. 3 *Duodenal ulcer. Comparison of mean serum levels of carbenoxolone when Duogastrone capsules were administered with antacid (●) in four patients and without antacid (○) in four patients.*

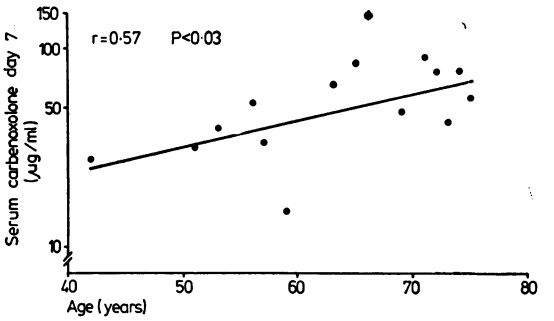

Fig. 4 *Correlation of serum carbenoxolone on day 7 with age in 15 patients with gastric ulcer treated with Biogastrone 300 mg/day for seven days. For log serum carbenoxolone* $r = 0{\cdot}57$, $P < 0{\cdot}03$; $y = 0{\cdot}014X + 0{\cdot}795$.

tablets 300 mg a day for seven days, and then 150 mg per day for the next three weeks, showed similar blood levels in the last three weeks compared with those receiving 300 mg per day throughout the four week course. However, the patients receiving 300 mg/day throughout had a minimum age of 58 years. Those on the lower dose for the last three weeks had a minimum age of 70 years, and for that reason might have tended to have a high serum level.

BLOOD LEVELS ON DAY 7 AND SUBSEQUENT WEEKS

There was a significant correlation (rho = 0·61, $P < 0{\cdot}02$) between the concentration of carbenoxolone in serum on the seventh day and the highest concentration achieved during the subsequent weeks of treatment. It will be seen from Figs. 1 and 2 that a steady state is probably not reached until day 14, so that representative values for carbenoxolone used in the calculations have been expressed both as the highest level and as the mean for days 7 + 14 + 21 + 28.

SERUM CARBENOXOLONE AND ULCER HEALING

The mean serum carbenoxolone on days 7-28 in nine patients whose gastric ulcers had healed completely endoscopically was almost identical with that in three patients whose ulcers had not completely healed. The patient whose duodenal ulcer had not healed after four weeks had a mean serum carbenoxolone on days 7-28 of 8 μg/ml, whereas the levels of three patients whose duodenal ulcers had healed completely were 23, 33, and 103 μg/ml.

SERUM CARBENOXOLONE AND SIDE-EFFECTS

Serum carbenoxolone concentrations in 13 patients who developed oedema were significantly higher than in the eight patients who did not (Table 3). There were no significant correlations between mean or highest serum carbenoxolone and weight gain, or with the greatest rise in either systolic, diastolic, or mean blood pressure. There were highly significant correlations between mean or highest serum carbenoxolone and change in plasma potassium (Fig. 5). Plasma potassium fell by more than 1 mmol/l in only one of 12 patients with mean serum carbenoxolone of less than 50 μg/ml, but in five out of eight patients with mean serum carbenoxolone of more than 50 μg/ml.

HEALING AND SIDE-EFFECTS

Twelve of the 15 patients with gastric ulcer agreed to repeat endoscopy after four weeks treatment. In nine patients the ulcers had healed completely, and, of these, four patients had oedema, and five had not.

Table 3 *Oedema and serum carbenoxolone in patients with gastric and duodenal ulcer*

	Serum carbenoxolone (μg/ml) in days 7-28 of treatment					
	Oedema 13		*No oedema 8*			
	Mean	*SD*	*Mean*	*SD*	*t*	*P*
Log mean	1·89	0·18	1·54	0·42	2·24	0·04
Log highest	1·99	0·19	1·70	0·39	1·98	0·06

Of the three patients whose ulcers had not healed completely, one had oedema, and two had not. In the patients whose gastric ulcers healed the mean weight gain (3·6 kg), rise in blood pressure (47/9 mm), and mean and fall in plasma potassium (3·0 and 0·9 mmol/l) were similar to those in patients with unhealed ulcers (4·1 kg, 37/15 mm, 3·1 and 0·8 mmol/l). Only four of the eight patients with duodenal ulcer agreed to repeat endoscopy.

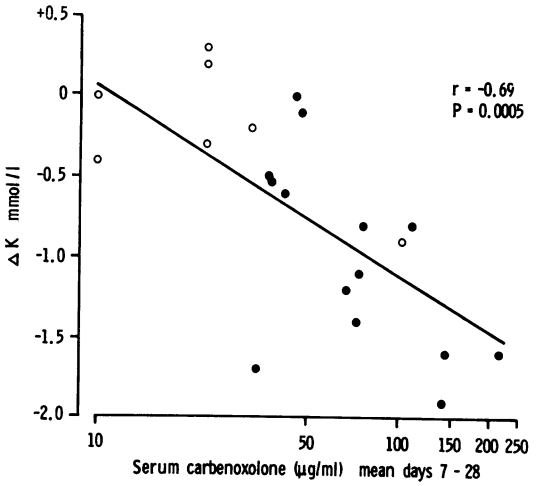

Fig. 5 *Correlation of mean serum carbenoxolone on days 7-28 with the maximum change in plasma potassium in 14 patients with gastric ulcer (●) and seven patients with duodenal ulcer (○). For log serum carbenoxolone* $r = -0{\cdot}69$, $P = 0{\cdot}0005$; $y = -1{\cdot}19X + 1{\cdot}27$. *(For log highest serum carbenoxolone,* $r = -0{\cdot}65$, $P = 0{\cdot}001$*).*

The ulcers of two of the three patients without oedema had healed, as had the ulcer of the one patient who had developed oedema. Patients with duodenal ulcer whose ulcers had, or had not, healed completely showed similar metabolic changes.

INTER-RELATIONSHIP OF SIDE-EFFECTS

The mean weight gain of 4·2 kg in seven patients who developed oedema was significantly greater ($P = 0{\cdot}03$) than the mean gain of 0·9 kg in patients who did not develop clinical oedema. However, there were no significant correlations between weight gain and increase in mean blood pressure or change in plasma potassium. It will be seen from Tables 1 and 2 that parallelism between weight gain and oedema was incomplete, so that serum carbenoxolone was related to oedema but not correlated with weight gain.

Discussion

FORMULATION, DOSE, MEALS AND ANTACIDS

The early studies of the absorption of carbenoxolone (Downer *et al.*, 1970; Lindup *et al.*, 1970; Parke *et al.*, 1972) had suggested that absorption was delayed by giving the drug in a buffer at pH 8·5 or after food. The present studies confirmed our previous findings that, while there was a delay in the initial absorption period in patients with gastric ulcer taking carbenoxolone as Biogastrone tablets after meals, there were no significant differences in subsequent days and weeks (Fig. 1). Concurrent antacid did not significantly affect blood levels of carbenoxolone in patients with gastric (Fig. 2) or duodenal ulcer except for the initial absorption period (Fig. 3). The serum half-life of carbenoxolone calculated from the initial absorption patterns in the patients with gastric ulcers showed no effects of meals or antacids (Baron *et al.*, 1975). The mean half-life of 13·2 hours in seven patients with gastric ulcer with a mean age of 58 years (Baron *et al.*, 1975) was comparable with those reported by Hayes and Langman (1975) in healthy subjects aged under 40 years (16·3 hours) but lower than those over 65 years (26·3 hours). These results support the contention that carbenoxolone as Biogastrone tablets need not be given at any fixed time in relation to meals, and that antacid administration is unlikely to affect the absorption of carbenoxolone from Biogastrone tablets or Duogastrone capsules.

The lower steady state serum levels of carbenoxolone after Duogastrone capsules (200 mg/day) than after Biogastrone tablets (300 mg/day) throughout the four weeks (Fig. 4) may be due to lower dosage of drug, because, although the separate group of patients with gastric ulcer treated in weeks 2 to 4 with 150 mg carbenoxolone per day had blood levels similar to those continuing to receive 300 mg/day, those on the lower dose were also older. The lower levels after Duogastrone may also reflect reduced absorption of the drug from the duodenum associated with delay in disintegration of the gelatin capsule (Galloway, 1968) and delivery of the drug to the duodenum rather than the stomach. Although blood levels of carbenoxolone varied markedly between patients, the skew distribution could be log normalised, and the mean or highest level of carbenoxolone reached in the last three of the four weeks' treatment depended on the level in that individual patient on the seventh day.

ULCER HEALING

There were no significant differences in the serum carbenoxolone levels between patients with gastric ulcers which healed and did not heal, but the

numbers of patients are small. The only controlled study (Doll *et al.*, 1968) showed significantly greater healing in patients treated with 300 mg/day than with 150 mg/day, but serum levels were not measured. Unfortunately, it is not known whether carbenoxolone exerts its ulcer healing effects topically or systemically, and further dose-response studies with measurements of blood levels are needed.

SIDE-EFFECTS

Side-effects with carbenoxolone are thought to be dose-related (Turpie and Thompson, 1965; Doll *et al.*, 1968), and in the present study patients developing oedema had significantly higher carbenoxolone levels than those remaining free of oedema, and the fall in plasma potassium was significantly correlated with the mean or highest serum carbenoxolone (Fig. 5). Because the two different doses of Biogastrone tablets (300 mg and 150 mg of carbenoxolone per day) achieved similar blood levels, the lower dosage is not necessarily any safer than the higher dose in producing side-effects in patients over 60 years of age.

AGE

The rise in serum carbenoxolone with age (Fig. 4) is presumably due to older patients having lower serum albumin, fewer binding sites, and decreased rates of plasma clearance of carbenoxolone (Hayes and Langman, 1975). The correlation of serum carbenoxolone with age as well as with side-effects, provides a rational explanation for the well-known clinical impression that side-effects are common in the elderly. Serum concentrations of carbenoxolone greater than 50 μg/ml were found after seven days' treatment particularly in patients over 60, and in subsequent weeks such levels of serum carbenoxolone were usually associated with hypokalaemia.

ULCER HEALING AND SIDE-EFFECTS

In the present study, and in that of Doll *et al.* (1968), there was no correlation between ulcer healing and clinical or metabolic side-effects. If further series confirm that ulcer healing is dose-dependent but independent of serum level, and side-effects dependent on both dose and serum level but independent of ulcer-healing, then further consideration must be given to the hypothesis that the ulcer-healing effect of carbenoxolone is topical rather than systemic.

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