The effect of phenylbutazone (Butazolidin) on plasma pepsinogen activity

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SYNOPSIS Phenylbutazone in moderate dosage has been administered to 15 patients with a variety of musculo-skeletal disorders. A rise in plasma pepsinogen activity occurred in 13, generally reaching a peak in the first week of treatment; subsequently there was a fall in spite of maintaining a constant dosage. In four of six patients an anticholinergic drug failed to prevent a rise in plasma pepsinogen activity.

These findings are considered in relation to clinical observations on the time of appearance of gastrointestinal side-effects in patients receiving phenylbutazone.

The interpretation of the findings is discussed, and it is suggested that the rise in plasma pepsinogen activity induced by phenylbutazone may reflect either increased peptic activity in the stomach or a damaging effect of the drug on the stomach.

Phenylbutazone is a synthetic pyrazolone compound resembling aminopyrin in chemical structure. It is widely used in the treatment of arthritis and musculo-skeletal disorders as it has analgesic and anti-inflammatory properties.

Among its several side-effects, those on the gastrointestinal tract are particularly common. Although stomatitis, constipation, and diarrhoea may occur, the most frequent complaints are of epigastric discomfort and nausea (Kuzell, Schaffarzick, Naugler, Gaudin, and Mankle, 1953). These symptoms may be associated with reactivation of peptic ulcers, and such lesions may be complicated by haemorrhage or perforation (Kirsner, 1957). Multiple superficial ulcers in the stomach have also been reported (Dilling, 1953). On the other hand, no lesion may be detectable in the stomach to account for the symptoms.

There have been few studies of the mechanisms by which phenylbutazone provokes epigastric discomfort and peptic ulceration. Kirsner and Ford (1955) showed that the secretion of acid rose significantly in 30 of 57 studies in 49 patients with single doses of 200 to 600 mg. Phenylbutazone intramuscularly in single doses of 50 to 400 mg. increased gastric acidity in 10 of 30 studies on 29 patients. These results have been confirmed by Bellomo and Fusco (1956). Neither the effect of repeated doses of phenylbutazone on gastric acidity in man nor its

effect on peptic cell activity appears to have been investigated.

This investigation is concerned with the effect of repeated doses of phenylbutazone on plasma pepsinogen activity in man.

METHODS AND MATERIALS

Phenylbutazone was first given to nine women with various musculo-skeletal disorders (Table I). Patient 6

TABLE I
PATIENTS TREATED WITH PHENYLBUTAZONE

	Age in Years	Diagnosis	Duration of Treatment in Days
Patient 1 (L.W.)	19	Sacro-iliac strain	7
Patient 2 (M.M.)	44	Intervertebral disc lesion	21
Patient 3 (L.L.)	65	Osteoarthritis of hip	15
Patient 4 (H.S.)	18	Tenosynovitis of wrist	21
Patient 5 (Y.B.)	20	Postural backache	25
Patient 6 (A.M.)	50	Lumbar spondylosis	84
Patient 7 (J.McN.)	19	Postural backache	9
Patient 8 (J.M.)	18	Postural backache	7
Patient 9 (D.A.)	26	Postural backache	11

had received phenylbutazone three years previously; otherwise no patient had received the drug before. Initially, 400 mg. was given orally in two divided doses; in patients 1, 2, 3, 4, and 7 this was reduced to 100 mg. three times daily after the first two days. The patients

were instructed to take the tablets immediately after meals.

The duration of treatment varied. It was not considered justifiable to continue the use of a potentially dangerous drug when a discernible therapeutic effect was not produced in one to three weeks. The drug was stopped in patient 1 after one week because of an erythematous rash, after 11 days in patient 9 because the patient complained of epigastric discomfort, and after 84 days in patient 6 because of the development of oedema.

A second group of six patients was then studied (Table II). Each was given either 300 mg. or 400 mg. of phenyl-

TABLE II
PATIENTS TREATED WITH PHENYLBUTAZONE
AND ANTRENYL

	Age in Years	Sex	Diagnosis	Duration of Treatment (Days)
Patient 10 (A.D.)	65	F	Osteoarthritis of hip	14
Patient 11 (E.M.)	60	F	Generalized osteo- arthritis	14
Patient 12 (F.H.)	74	M	Lumbar spondylosis	14
Patient 13 (T.B.)	30	F	Polyarthritis ? cause	7
Patient 14 (F.W.)	28	M	Reiter's syndrome	7
Patient 15 (E.T.)	66	F	Rheumatoid arthritis	14

butazone daily for one to two weeks, and in addition an anticholinergic drug. The anticholinergic drug used was oxyphenonium bromide (Antrenyl), 5 mg. being administered orally four times daily. These patients also received magnesium trisilicate powder, 4 ml. three times daily after meals.

In both groups plasma pepsinogen activity was measured twice before the drug was started and at

FIG. 1. Average values for nine patients receiving phenylbutazone alone (baseline = 250 units).

intervals during treatment. Blood was taken at the same time on each day to avoid possible diurnal variations, and the plasma was stored at -15°C .

Mirsky's modification of Ansen's method of estimating tyrosine substances formed during enzymatic proteolysis was used (Mirsky, Futterman, Kaplan, and Broh-Kahn, 1952; Hoar and Browning, 1956). A series of standard solutions of tyrosine was included in each assay, as the Folin-Ciocalteu colour reaction is not constant. A Hilger absorptiometer as used by Nolan (1958) was used at a wave length of 430μ . Results are expressed in tyrosine

TABLE III
PATIENTS TREATED WITH PHENYLBUTAZONE ALONE

Patient		1	2	3	4	5	6	7	8	9	Mean for 9 Cases
Before butazolidin	Day 1	400	320	480	290	320	300	290	310	570	
	Day 2	380	305	440	295	280	270	340	400	520	
	Mean before	390	312.5	460	292.5	300	285	315	355	545	361.6
During butazolidin	Day 3	400	345		330	390	460			565	
	4			540					410		
	5	500	475		400		520			620	
	6			480		370		350			
	7	475	400		310		450			500	
	8			520		430		330			
	9		350								
	11									550	
	14		380		350	460	340				
	15			440							
	21		310		280	350	410				
	52						450				
	84						280				
Mean during		458	377	495	334	400	416	340	410	557	411.2
After butazolidin	1	355	300	—	300	290	380	260	390	550	
	2	350	320								
	Mean after	352.5	310	—	300	290	380	260	390	550	354.5 (For 8 cases)

Plasma pepsinogen activity expressed as tyrosine units released per ml. of plasma.

FIG. 2. The effect of phenylbutazone on plasma pepsinogen activity in patients 2 and 4 (baseline = 200 units).

FIG. 3. The effect of phenylbutazone on plasma pepsinogen activity in patients 5 and 6 (baseline = 200 units).

units, equivalent to microgrammes of tyrosine released per millilitre of plasma. The variation between duplicate estimations was found to be less than 7%.

RESULTS

The results in the first nine patients are shown in Table III and illustrated in Fig. 1. In all cases pepsinogen activity rose during treatment. The difference between the mean before and during treatment is highly significant ($P=0.001$). After treatment the values fell to pre-treatment levels.

Table III also shows that there was a tendency for the values to be highest during the first week of

treatment. Thereafter they tended to fall towards pre-treatment levels in spite of a constant intake of phenylbutazone. The results in the four patients who were most completely studied over long periods are shown diagrammatically in Figs. 2 and 3.

The results in the patients in the second group are shown in Table IV. Plasma pepsinogen activity rose in patients 10, 11, 13, and 15, despite the administration of an anticholinergic drug.

DISCUSSION

It has been recorded that epigastric discomfort and ulcer complications induced by phenylbutazone

TABLE IV
PATIENTS TREATED WITH PHENYLBUTAZONE AND ANTRENYL

Patient		10	11	12	13	14	15	Mean for 6 Cases
Before	Day 1	180	310	300	235	400	270	
butazolidin	Day 2	190	290	290	245	450	—	
Mean before		185	300	295	240	425	270	285.8
During	Day 3	190	350	220	250	460	330	
butazolidin	5	290	360	290	320	320	420	
	7	220	330	300	150	370	275	
	14	250	370	270	—	—	360	
Mean during		237.5	352.5	270	273.3	383.3	346.25	310.5

Plasma pepsinogen activity expressed as tyrosine units released per ml. of plasma.

occur most frequently early in the course of treatment (Kelly, 1954; Mauer, 1955). In one group of 35 patients with these side-effects, 23 developed symptoms in the first week (Freeland, Storey, and Thompson, 1953). Less commonly ulcer symptoms may develop after months of treatment. Reactions have also occurred after the drug has been withdrawn, and in this connexion it is interesting that phenylbutazone remains in the blood for 10 to 21 days after cessation of treatment (Bruck, Fearnley, Meanock, and Patley, 1954). The results recorded here, showing a peak rise in plasma pepsinogen activity during the first week of administration of phenylbutazone with a subsequent fall, may be relevant to the clinical observation of the time of greatest frequency of these gastrointestinal side-effects.

To draw more specific conclusions from these results depends on the interpretation of the relationship between levels of plasma pepsinogen activity and gastric function. The exact relation between peptic cell activity and plasma pepsinogen activity is uncertain. There is a virtual absence of pepsinogen activity in plasma and urine following total gastrectomy and in cases of pernicious anaemia (Chinn, 1953; Hirschowitz, 1955). Conversely, gastric pepsin secretion and plasma pepsinogen activity are both significantly higher in patients with duodenal ulcer than in normal persons (Chinn, 1953; Van Goidsenhoven, Wilkoff, and Kirsner, 1958). In addition, significant correlations have been shown between gastric pepsin and plasma pepsinogen activity in normal people by Janowitz, Levy, and Hollander, (1950) and Van Goidsenhoven *et al.* (1958).

Hirschowitz (1957) has stressed the constancy of plasma pepsinogen activity despite such stimuli as food, insulin, and anticholinergic drugs, all of which modify gastric pepsin secretion. He does not believe that the plasma activity gives a reliable indication of the secretory activity of the stomach. Goidsenhoven has, however, pointed out that the general pool of pepsinogen in the body may be quite large and it may therefore take some time for stimuli to affect the plasma activity. Thus, starvation for 24 to 48 hours and a similar duration of treatment with

anticholinergic drugs is necessary to decrease plasma activity. The changes reported here may therefore reflect increased peptic cell activity.

An alternative explanation for our findings is suggested by an observation by Hirschowitz (1957). He found that plasma pepsinogen activity is increased by procedures which damage the gastric mucosa, such as destructive doses of histamine in dogs and guinea-pigs. He suggested that the rise in plasma pepsinogen in these circumstances was analogous to the rise in plasma of pancreatic enzymes following acute pancreatitis. It is possible, therefore, that the early rise in plasma pepsinogen activity which follows administration of phenylbutazone may reflect damage to the stomach rather than a change in secretory activity, and this possibility merits further study.

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