The uricosuric action of azapropazone: dose-response and comparison with probenecid

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1 Azapropazone is an anti-inflammatory agent with reported uricosuric properties. The aim of the present study was to extend these observations, by examining the dose-response and to compare the uricosuric effect of azapropazone with that of probenecid.

2 Patients were given varying doses of azapropazone from 900–2400 mg daily for 4-day periods at separated intervals. Plasma uric acid levels were measured before and at the end of each treatment period. Three other patients maintained on low purine diets were given a 4-day course of 1200 mg azapropazone daily followed at an interval by a 4-day period of probenecid 1 g daily. Plasma uric acid levels and 24 h urinary uric acid excretion were compared.

3 The mean fall in plasma uric acid level after four days of 900 mg azapropazone daily was 31.4% ($n = 9$) compared with 33.9% ($n = 12$) on 1200 mg daily; 42.3% ($n = 10$) on 1800 mg daily; and 46% ($n = 6$) on 2400 mg daily, indicating a graded dosage response.

4 In the three patients on low purine diets the falls in plasma uric acid levels on probenecid 1 g daily were 50.5%, 46% and 29% compared with 33.5%, 32% and 20% respectively on azapropazone 1200 mg daily. Similarly the total amount of uric acid excreted in the urine by each patient during the 4-day period on probenecid 1 g daily was 14.01; 13.03 and 8.97 mmol compared with 23.53, 10.9 and 7.69 mmol on azapropazone 1200 mg daily.

5 In one patient who received further 4-day treatment periods on 900 mg, 1800 mg and 2400 mg azapropazone daily the hypouricaemic and uricosuric effect of 1800 mg and 2400 mg azapropazone and probenecid 1 g daily were comparable.

6 A daily dose of azapropazone 1200 mg is less effective than probenecid 1 g daily, whereas doses of 1800 mg and 2400 mg have a comparable uricosuric effect.

7 Azapropazone has thus been shown to possess a dose-related uricosuric action.

Keywords azapropazone uricosuric dose-response probenecid

Introduction

Conventional drug treatment for gout is of two types. In the first place, alleviation of acute pain and inflammation is achieved by the use of colchicine or a potent non-steroidal anti-inflammatory drug (NSAID). Secondly, where indicated, the long-term reduction of plasma uric acid levels is achieved with a hypouricaemic

agent to prevent and reverse crystal deposition (Scott, 1980).

Most NSAIDs used for acute gout do not affect uric acid metabolism. An important exception is phenylbutazone, which is not however prescribed for gout over prolonged periods because of its relatively weak uricosuric effect and potential toxicity. Aspirin is also unsatisfactory because of the high doses neces-

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sary to sustain a uricosuric action (Yu & Gutman, 1959). A drug possessing both significant hypouraeic and anti-inflammatory properties is of obvious interest and potential importance in the management and prevention of gout.

Azapropazone, a pyrazolidine ring derivative (analogous to phenylbutazone), has a potent anti-inflammatory action, and is well-estimated in the treatment of rheumatoid arthritis and osteoarthritis (Hart, 1978). It has also been shown to have a significant hypouricaemic effect (Herne *et al.*, 1977) and uricosuric action (Frank, 1971) with maximal effect by the fourth day of treatment.

Preliminary studies showed that azapropazone is effective in acute gout (Thomas *et al.*, 1979; Dieppe *et al.*, 1981; Templeton, 1983). However, its mechanisms of action and effect on renal function are still unclear.

The aims of the present studies were to confirm the hypouricaemic and uricosuric properties of azapropazone; to define whether the effects were dose related; and to compare azapropazone and probenecid as uricosuric agents.

Methods

Twenty subjects, consisting of 16 patients with quiescent gout and four normouricaemic volunteers, not currently taking a hypouricaemic or anti-inflammatory agent, were admitted to the first part of the study. Seventeen were men and three women. None had evidence of renal failure or renal stones.

The patients were taking a normal diet as outpatients. Each received a maximum of four different treatment periods of azapropazone, separated by intervals off treatment. The order of treatment periods for each patient was randomly allocated. A treatment period con-

sisted of 4 days on either 900 mg, 1200 mg, 1800 mg or 2400 mg daily.

Plasma uric acid levels were measured before and at the end of each treatment period, being estimated by a manual enzymatic uricase assay (Liddle *et al.*, 1959).

In the first part of the study the dose response to azapropazone was expressed as a percentage fall in plasma uric acid levels during each of the treatment periods.

In the second part of the study three normouricaemic patients were maintained as in-patients on low purine, low caffeine, alcohol-free diets. The three patients were receiving hospital treatment for rheumatoid arthritis, and were receiving no other anti-inflammatory drug during the period of the study. They were each given 1200 mg azapropazone for 4-day courses followed at an interval (during which plasma and urinary urate levels regained their original values) by a 4-day period of probenecid 1 g daily. Plasma uric acid levels and 24 h urinary uric acid excretion rates were compared. One patient received varying doses of azapropazone (600 mg, 1200 mg, 1800 mg, 2400 mg) for 4-day courses to compare with probenecid 1 g daily. The other two each received two courses of azapropazone 1200 mg daily.

Changes in serum creatinine during and after treatment periods were estimated and any side effects of azapropazone and probenecid were noted.

Results

The mean pretreatment plasma uric acid level of the 20 patients who participated in the first part of the study was $397 \mu\text{mol/l} \pm 73.8$. In total, 37 4-day treatment periods on azapropazone were completed. The mean plasma uric acid concentrations at the start and end of each treatment period are shown in Table 1. There is clearly a graded response to azapropazone.

Table 1 Dose-response to azapropazone (mean $\pm$ s.d.)

	Dose of azapropazone daily (mg)				
	900	1200	1800	2400	Total
Number of treatment periods	9	12	10	6	37
Mean starting PUA ($\mu\text{mol/l}$)	417 ± 93.1	375 ± 75.9	409 ± 61.7	387 ± 59.6	397 ± 73.8
Mean finishing PUA ($\mu\text{mol/l}$)	285 ± 78.8	245 ± 56.8	234 ± 46.4	207 ± 38.5	246 ± 61.5
Mean % fall in PUA	31.4 ± 14.0	33.9 ± 9.9	41.4 ± 9.2	46.0 ± 9.0	37.5 ± 11.8

Table 2 Comparison of uricosuric effects shown by azapropazone 1200 mg daily and probenecid 1 g daily in three subjects

	Patients		
	1	2	3
Mean PUA before treatment ($\mu\text{mol/l}$)	367	329	242
% fall in PUA on azapropazone 1200 mg/day for 4 days	33.5	32	20
% fall in PUA on probenecid 1 g/day for 4 days	50.5	46	29
<i>Total 4 day uric acid excretion (mmol)</i>			
Baseline period	7.8	6.5	7.2
On azapropazone 1200 mg/day	12.5	10.9	7.7
On probenecid 1 g/day	14.0	13.0	9.0

Response to the drug expressed as the percentage fall in plasma uric acid, was independent of the initial plasma uric acid level: i.e. it was similar in hyperuricaemic and normouricaemic subjects for each dosage treatment and overall (Student's *t*-test).

Results of the second part of the study (during which three normouricaemic patients on low purine diets took 1200 mg azapropazone for a 4-day period and probenecid 1 g daily for a separate 4-day period) are shown in Table 2. It is seen that at these doses probenecid has a more potent uricosuric action.

The effect of azapropazone 1200 mg daily

was reproducible, and shown for one patient in Figure 1. In patient 2 a graded uricosuric and hypouricaemic response to azapropazone was demonstrated (Figure 2). Azapropazone 1800 mg and 2400 mg daily had comparable effects to that of probenecid 1 g daily.

Levels of plasma creatinine before and after 31 treatment periods with varying doses of azapropazone showed a slight rise after the drug. The effect was maximal with the dose of 2400 mg daily, but levels returned to pretreatment figures later (Table 3).

All patients were also asked about gastrointestinal symptoms associated with azapropa-

Figure 1 Reproducible uricosuric and hypouricaemic effect of an azapropazone 1200 mg/day in patient 1.

Figure 2 Graded uricosuric response to azapropazone in patient 2.

zone treatment. Few side effects were forthcoming. One patient had to stop taking 1800 mg daily due to severe dyspepsia. A further six patients had mild gastrointestinal symptoms (16%).

Discussion

This study confirms the reproducible hypouricaemic effect of azapropazone and demonstrates a graded dose response.

The mode of hypouricaemic action has been questioned. Previous data from Frank (1971) showed a consistent uricosuric effect but Gibson *et al.* (1984) found the rise in urinary acid

excretion associated with azapropazone treatment to be insufficient to explain the consistent hypouricaemic action. They, with Herne *et al.* (1977), questioned whether some other mechanism was operative, perhaps associated with the prostaglandin inhibiting effect of a NSAID with consequent fluid retention and fall in creatinine clearance. It has, however, been shown that uricosuric agents exhibit different degrees of effectiveness in different patients probably due to variation in fluid intake and output during treatment (Emmerson, 1963). This may explain some of the inconsistencies. Our data indicate that the uricosuric effect is at least the principal mode of action with a dose of 1800 mg and 2400 mg as potent as probenecid 1 g daily.

Table 3 Changes in serum creatinine after 4-day treatment periods with azapropazone

Dose (mg/day)	Number of treatment periods	Mean serum creatinine	
		Pre-treatment (mmol/l)	After treatment (mmol/l)
900	7	97.5 ± 22.0	114.6 ± 22.5
1200	11	93.8 ± 19.0	114.9 ± 18.7
1800	9	101.8 ± 18.2	112.1 ± 22.8
2400	4	100.8 ± 17.2	128.8 ± 36.9
All	31	97.9 ± 18.6	*115.8 ± 22.8

* difference significant $P < 0.001$ (paired *t*-test)

(Not all patients had serum creatinine levels measured therefore numbers differ from total)

Azapropazone has the superficially attractive property of combining anti-inflammatory with uricosuric properties, thus being suitable for both the treatment of acute gout and the long-term control of hyperuricaemia. However, there are reservations to this concept. In the first place, immediate control of hyperuricaemia is not necessarily desirable during treatment of the first acute attack: not only may this prevent adequate assessment of uric acid levels, but rapid lowering of serum urate may actually induce and prolong acute attacks, although Dieppe *et al.* (1981) found that acute attacks of gout treated with azapropazone lasted no longer than those treated with other anti-inflam-

matory agents. Secondly, while it is customary to prescribe an anti-inflammatory drug during the first month or two of urate-lowering treatment, this is not usually necessary once hyperuricaemia has become consistently controlled and the patient is free of symptoms.

Azapropazone in moderate dosage (1200 mg) does not appear to be as potent a hypouricaemic agent as probenecid. Its combined anti-inflammatory and uricosuric actions may be useful for some gout sufferers but to what extent azapropazone will replace our other very effective methods of treatment of gout remains to be seen.

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