Comparative trial of azapropazone and indomethacin plus allopurinol in acute gout and hyperuricaemia

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SUMMARY. This study compared the effects of azapropazone and indomethacin plus allopurinol in the management of acute gout and hyperuricaemia. A group of 93 patients predominantly based in general practice were randomly allocated to the two treatment regimens (azapropazone (days 1–225) or indomethacin (1–28) followed by allopurinol (29–225)) on a double-blind double dummy basis. Azapropazone produced a substantial reduction in serum uric acid levels by day 4 compared with day 1 ($P<0.002$) and was superior to indomethacin with regard to recorded levels of serum uric acid at day 4 ($P<0.01$) and day 28 ($P<0.05$). From day 28 onwards allopurinol produced and azapropazone maintained similar reductions in serum uric acid. Both treatments rapidly controlled the initial acute attacks of gout and both produced side effects similar in frequency and nature. Fewer breakthrough attacks of gout occurred in the azapropazone group (12) than the indomethacin/allopurinol group (21).

Although the results achieved in both treatment groups were similar it has been shown that azapropazone is effective monotherapy for controlling both acute attacks of gout and hyperuricaemia.

Introduction

THE main therapeutic challenge in the management of an acute attack of gout is to alleviate pain as quickly as possible. The principal longer term aim is to prevent the occurrence of further attacks by removing the underlying cause of the disorder which is an excess of uric acid in the body, the 'biochemical hallmark'[1] of which is hyperuricaemia. If the latter objective can be achieved there is a likelihood that the development of complications of the disease can be prevented.

At present, indomethacin, a non-steroidal anti-inflammatory agent, is the analgesic most often used to control the pain of an acute attack of gout, whereas allopurinol, a xanthine oxidase inhibitor is the drug most commonly used to control hyperuricaemia. The usual practice is to introduce allopurinol once the acute pain has subsided and to discontinue indomethacin once the risk of allopurinol-induced acute gout has lessened. Allopurinol can, nevertheless, induce acute attacks of gout, particularly in the first few weeks of its use.[2]

On the other hand, azapropazone, as a non-steroidal anti-inflammatory drug, has been shown to be effective in controlling the symptoms of an acute attack of gout,[3,4] and as a uricosuric agent, in controlling hyperuricaemia.[5] Furthermore, there is some evidence that it can achieve this without inducing acute attacks of gout.[3]

Thus, a single drug, azapropazone, offers the possibility of controlling all aspects of gout along with a reduced risk of inducing recurrent acute attacks compared with conventional treatment. We report on a clinical trial which compared the outcome of using both these treatment regimens.

Method

Of the 93 patients admitted to the study most were recruited from general practices associated with two university departments of general practice, although eight patients were recruited from hospital outpatient departments. The patients were randomly allocated to two groups, whose treatment schedules are shown in Table 1. From days 1 to 85 the trial was double-blind using the double dummy method. From days 85 to 225 all patients continued the treatment in open fashion.

Patients of either sex and aged over 18 years were admitted to the study provided that they were suffering from an attack of acute gout sufficiently severe to justify treatment. The nature and purpose of the trial was explained to each patient and their consent obtained. Patients taking hypoglycaemic, anticoagulant or immunosuppressant drugs, and any patients taking phenytoin were excluded. Pregnancy, a history of peptic ulceration within 12 months and known sensitivity to any of the trial drugs also excluded a patient. A patient was to be withdrawn from the trial if the original diagnosis of acute gout was found to be incorrect, if the acute attack did not respond to treatment within five days or if the physician considered that an apparent side effect warranted this.

On day 1, the date and time of onset of the acute attack were recorded and blood taken for estimation of serum uric acid levels. Patients were thereafter seen on days 4, 28, 56, 85, 113, 141, 169, 197 and 225. On day 4 the date and time of initial relief of the acute attack was recorded, the patient was asked, 'Did the treatment suit you?' and blood was taken for estimation of serum uric acid. On all subsequent occasions they were asked the same question, blood was taken for estimation of serum uric acid and they were asked, 'Have you had another attack of gout?' On day 85, when the double-blind period ended, they were asked, after discussion, 'Do you want to continue with the treatment?' Any other drugs taken during the trial were recorded.

Table 1. Study treatment schedules.

Time (days)	Group A ($n=47$)	Group B ($n=46$)
1	Indomethacin 100 mg stat 50 mg 2 hours later 50 mg 3–4 hours later	Azapropazone 600 mg tds
2–4	50 mg tds	600 mg tds
5–28	25 mg tds	600 mg bd
29–225	Allopurinol 150 mg bd	600 mg bd

n = number of patients enrolled in study.

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Results

Forty-six of the patients received azapropazone and 47 indomethacin followed by allopurinol. Both groups were similar in terms of age and sex composition. One patient receiving indomethacin was withdrawn at day 28 because of doubt about the original diagnosis of gout.

The initial treatment for the acute gout attack was favourably received by 40 of the patients receiving azapropazone and 35 of the patients receiving indomethacin (that is the patients answered 'yes' to the question: 'Did the treatment suit you?'). These differences were not statistically significant (chi-squared test). No patients were withdrawn from the study within the first five days because of failure to control the symptoms of the acute attack.

A comparison of the mean serum uric acid measurements during the study is shown in Figure 1. At the initial visit, there was no significant difference in serum uric acid between the groups, but at 4 and 28 days the patients in the azapropazone treated group had significantly lower serum uric acid than the patients in the indomethacin treated group ($P<0.01$ and $P<0.05$, two-sample 't' test). The differences between the two treatment groups were not statistically significant for days 56 to 225. In the group receiving azapropazone, significant falls within the group were observed ($P<0.002$, Wilcoxon signed-rank test) for all time periods up to day 225. In the group receiving indomethacin/allopurinol the fall in serum uric acid was significant only after the start of allopurinol treatment (that is after 28 days).

During the period of the study, 33 patients experienced 49 acute attacks of gout; 12 of the patients were taking azapropazone, 21 indomethacin/allopurinol. The timing of the acute attacks is shown in Table 2. In addition a further six patients (three on azapropazone, three on indomethacin) experienced 'twinges', rather than acute gout attacks.

Ten patients in the indomethacin/allopurinol group left the study because of suspected adverse reactions while taking indomethacin and two left the study while taking allopurinol. Twelve patients in the azapropazone group left the study (eight during the first 28 days) because of suspected adverse reactions. The adverse reactions encountered (which were mainly related to disturbances of the gastrointestinal tract) are shown in Table 3.

Discussion

This comparison of two regimens for treating acute gout and subsequent control of hyperuricaemia shows that both resulted in adequate control of the acute attack and both produced satisfactory reductions of serum uric acid levels.

Flare-up of acute gout occurred more frequently in patients taking indomethacin followed by allopurinol than in patients taking azapropazone. Attacks in the indomethacin/allopurinol group were most common between days 28–56 of the study, partly because indomethacin therapy was stopped when allopurinol was started. However, five attacks occurred in the first 28 days while patients were taking indomethacin alone as against one on azapropazone. This would suggest that the lower serum urate produced by the azapropazone lessened the likelihood of further attacks in the initial weeks of treatment.

Treatment of an acute attack of gout with non-steroidal anti-inflammatory drugs can result in gastrointestinal side effects no

Table 2. Timing of acute attacks of gout.

	Day							
Treatment	28	56	85	113	141	169	197	225
Azapropazone	1	4	4	1	2	4	0	3
Indomethacin/allopurinol	5	9	2	6	2	2	2	2

Table 3. Suspected adverse reactions leading to withdrawal from the trial.

Treatment	Gastro-intestinal	Rash	CNS	Cardiac failure	Abnormal LFT
Azapropazone	11[a]	1			
Indomethacin	6[b]		3	1	
Allopurinol		1			1

CNS = central nervous system. LFT = liver function tests.
[a]One patient developed a perforated duodenal ulcer on day 85.
[b]Gastrointestinal bleeding occurred in one patient (melaena).

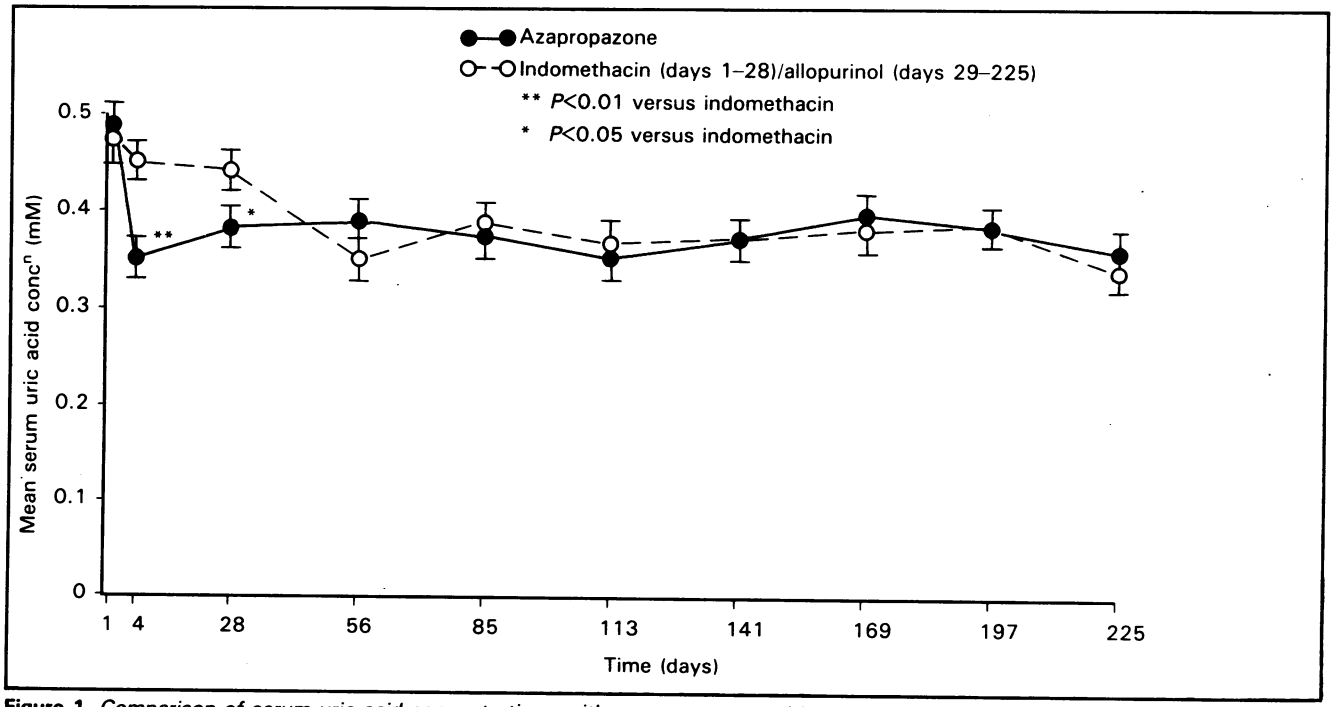

Figure 1. *Comparison of serum uric acid concentrations with azapropazone and indomethacin/allopurinol.*

matter which of these drugs is used. Such side effects occurred with both indomethacin and azapropazone in the first three weeks of the study, dyspepsia also occurring with azapropazone at six and at seven weeks.

This study shows that azapropazone can be used successfully as monotherapy for the control of both hyperuricaemia and acute gouty attacks.

References

1. Nuki G. Disorders of purine metabolism. In: Weatherall DJ, Readingham JGG, Warrell DA (eds). *Oxford textbook of medicine*. Oxford University Press, 1983.
2. Fox IH. Hypouricaemic drugs in the treatment of gout. *Clin Rheum Dis* 1977; **3:** 145.
3. Dieppe P, Doherty M, Whicher J, Walters G. The treatment of gout with azapropazone: clinical and experimental studies. *Eur J Rheumatol Inflamm* 1981; **4:** 392-400.
4. Gibson T, Simmons HA, Armstrong RD, *et al.* Azapropazone — a treatment for hyperuricaemia and gout? *Br J Rheumatol* 1984; **23:** 44-51.
5. Frank O. Investigation of the uricosuric action of azapropazone. *Z Rheumatol* 1971; **30:** 368-373.

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