receiving azapropazone and there was also a higher prevalence of abnormal renal function (judged by raised blood urea or serum creatinine or both) in this group. Analysis of the data on renal function, however, reveals that in the group treated with azapropazone the increase in urea or creatinine occurred principally during the first two weeks of treatment and did not rise further.

In addition, out of 32 patients changed to azapropazone who were receiving additional analgesics at the start of the study, 22 were able to stop this analgesic(s), 10 continued them, and five more had to start taking—usually intermittently—additional analgesics. Of 39 patients who continued taking allopurinol, nine were able to stop additional analgesics, nine continued on the same additional analgesics as before, and 21 had to start treatment with an additional analgesic.

Thus, azapropazone would appear to be a useful alternative drug for the long term control of patients with chronic gout or hyperuricaemia, or both. Its two possible important advantages are that it is a single drug treatment for acute and chronic gout and it provides a considerable measure of analgesic effect, which allopurinol cannot do, for those patients who have painful concurrent degenerative joint disease such as osteoarthritis, cervical spondylosis, backache, etc.

Table 1 *Serum urate concentration of treated patients (normal values 0·14–0·45 mmol/l)*

	Time (weeks) 0	4	8	12	16	24
Azapropazone:						
No of patients	133	122	106	108	90	96
Serum uric acid (mmol/l):						
Mean	0·385	0·375	0·383	0·388	0·401	0·396
SD	0·114	0·094	0·101	0·098	0·110	0·120
Allopurinol:						
No of patients	116		113		105	105
Serum uric acid (mmol/l):						
Mean	0·362		0·341		0·328	0·345
SD	0·150		0·106		0·084	0·103

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Gout with apparent resistance to allopurinol

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The dose of allopurinol necessary to induce sustained normouricaemia in gout rarely exceeds 300 mg daily. We describe a patient with apparent resistance to conventional doses of allopurinol and probenecid. The study was designed to evaluate the response to varying doses of allopurinol and to determine whether the hyperuricaemia and the reported lack of effect of allopurinol were related to some unusual disturbance of purine metabolism.

CASE REPORT

A 51 year old man had experienced intermittent episodes of gout confirmed by the demonstration of intra-articular urate crystals for 20 years. Various combinations of anti-inflammatory and hypouricaemic drugs had failed to exert a detectable effect on his recurrent arthritis. At the time of referral he was obese but exhibited no tophi and was normotensive. One brother had a history of gout. His alcohol consumption was modest, though he had transient liver dysfunction; liver biopsy showed no abnormality. Glomerular filtration rate (^{51}Cr EDTA) was normal at 100 ml/min/1·73 m^2 but his urine was of constant pH and renal concentrating ability was impaired. He was admitted to hospital on three separate occasions for investigation. After four days on a low purine, caffeine free diet he underwent five periods of treatment with allopurinol in doses increasing from 200 mg to 1200 mg.

Each treatment period lasted a further four days except the last (1200 mg/day), which was curtailed after two days. The studies were conducted in a metabolic ward. Table 1 shows the results of daily investigations conducted before and during each treatment period. Estimations of uric acid, purines, and allopurinol metabolites were performed as previously described.[1,2] Red cell lysates were investigated for enzyme deficiencies, which are acknowledged

Table 1 *Results of investigations during three hospital admissions. On each occasion, the patient received a low purine diet for four days, without treatment, followed by varying doses of allopurinol*

Dose of allopurinol (mg)	*Plasma uric acid (mmol/l)*	*Urinary uric acid (mmol/24h)*	*Urate clearance (ml/min)*	*Total urine oxypurines (mmol/24h)*	*Urine hypoxanthine: xanthine ratio*	*Allopurinol metabolites (% of dose)*	*Plasma oxipurinol (μmol/l)*
0	0·70	4·7	4·7	4·96	3·3	—	—
200	0·76	3·4	3·1	3·92	1·5	26	—
0	0·67	4·2	4·4	4·3	3·5	—	—
300	0·86	1·5	1·2	1·74	2·4	8	17
600	0·85	1·92	1·6	2·22	1·6	7	50
0	0·66	4·3	4·5	4·43	0·83	—	—
900	0·45	4·4	6·9	4·82	0·66	7	20
1200	0·28	3·4	8·4	4·74	0·45	18	35

Conversion: SI to traditional units— Uric acid: 1 mmol/1 ≈ 17 mg/100 ml; 1 mmol/24 h ≈ 0·17 mg/24 h.

causes of hyperuricaemia. Red cell nucleotide concentrations were also estimated.[3]

On a low purine diet, plasma uric acid concentration was always grossly raised. Allopurinol in daily doses up to 600 mg caused a further rise in plasma urate, which was associated with a fall in excretion of uric acid and a concomitant reduction of urate clearance. Urate clearance corrected for creatinine clearance (not shown) also fell, suggesting that the rise in blood uric acid was secondary to impaired clearance. By contrast, with doses of 900 to 1200 mg plasma urate fell and urate clearance increased. During the first two admissions the ratio of urine hypoxanthine to xanthine was raised before treatment (normal < 1·5:1), suggesting increased de novo purine synthesis. Normally, allopurinol treatment results in an increase of urine hypoxanthine and especially of xanthine with a fall of their ratio to values of < 1·0:1. This was not observed, and the percentage of total allopurinol metabolites recovered in the urine was exceptionally low. On the other hand, plasma oxipurinol concentrations were consistent with those expected of patients receiving allopurinol.

Hypoxanthine guanine phosphoribosyl transferase (HGPRT), and phosphoribosylpyrophosphate synthetase (pPribose P synthetase) activities were normal as were erythrocyte nucleotide concentrations.

COMMENT

We have previously reported that this patient was unresponsive to conventional doses of allopurinol.[3] It is now apparent that high doses of the drug will reduce his blood concentration of uric acid. Others have noted that the daily dose of allopurinol necessary to produce nomouricaemia occasionally exceeds 300 mg,[4] but doses up to 1000 mg are sometimes necessary.[5] The anomalous results obtained in this study raise several questions. The low recovery of urine allopurinol metabolites suggests that the patient failed to ingest the allopurinol (unlikely under conditions on a metabolic ward) or did not absorb it. As plasma oxipurinol concentrations were in accord with those normally achieved after conventional allopurinol doses it is also possible that there was a failure to excrete metabolites in the usual fashion. The paradoxical rise in plasma uric acid on lower doses of allopurinol appeared to be caused by a further reduction of an already reduced urate clearance. The high hypoxanthine concentrations and the increased hypoxanthine to xanthine ratio suggest that the patient was an overproducer of uric acid. However, the normal enzyme and nucleotide concentrations would exclude any of the known causes of purine overproduction.

The lack of response to allopurinol and the low concentrations of urine metabolites are unique observations. Investigation of other patients requiring large doses of allopurinol may reveal identical anomalies. Patients whose unresponsiveness to allopurinol has been attributed to poor compliance may also be similar examples. It remains to be seen whether the patient described here is representative of a previously unrecognised group of patients with gout.

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