Controlled inpatient study of tienilic acid in treatment of gout and hypertension

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SUMMARY Under inpatient controlled conditions 4 patients with gout and hypertension were treated with varying doses of tienilic acid, a new uricosuric diuretic. Plasma urate levels were reduced by an average of 50% in association with significantly increased urinary urate excretion. A twice-daily regimen was considerably more effective than a single morning dosage in reduction of plasma urate, though both regimens were equally effective in antihypertensive potency. The single daily regimen produced greater diurnal fluctuations in plasma urate and was more frequently associated with the development of acute gout attacks.

Attention has previously been drawn to the unusually high prevalence of hypertension among patients with gout.¹⁻⁵ While a diastolic blood pressure of 90 mmHg or greater is found in approximately 21% of a similar nongouty population (males, aged 25-65), up to 50% of patients with gout will be so affected.⁶ Thiazide diuretics, a group of drugs commonly used for hypertension, elevate the serum uric acid level by virtue of their urate-retaining action.⁷ Control of hyperuricaemia and gout is thereby made more difficult requiring a large dose of urate-lowering drugs. In other patients, with hypertension alone, the effect of the thiazides may be to raise the serum level of uric acid and perhaps to precipitate an acute gout attack.⁸

A new diuretic, tienilic acid, has been reported to lower serum uric acid levels by increasing urinary excretion.^{9,10} Since these reports have been confined to primarily hypertensive patients, usually without hyperuricaemia, it was decided to investigate the drug in patients with previously diagnosed hyperuricaemia and gout as well as hypertension and to assess the potential for control of both conditions with a single agent.

Patients and methods

Four patients were admitted to hospital and maintained on a low-purine diet for the duration of the study. All were hyperuricaemic, and gouty arthritis had been previously diagnosed on generally accept-

able clinical grounds; hypertension (resting diastolic blood pressure 90 mmHg or greater) was confirmed on at least 3 occasions before admission. Throughout admission, resting and standing blood pressures were measured 4-hourly (except at 2 am). Estimations of uric acid levels were performed by a uricase method on plasma (8-hourly) and urine (4-hourly collections, except midnight to 8 am). Creatinine clearance, liver function tests, fasting cholesterol and triglycerides, full blood count, and erythrocyte sedimentation rate (ESR) were performed before and at the end of each admission.

Chest x-ray and electrocardiography (ECG) were carried out before beginning treatment. Serum electrolytes were measured frequently and total urinary electrolytes daily. Blood pressure and plasma and urine uric acid were monitored for several days, (average 6) following admission, until these were stabilised with bed-rest and the low-purine diet. Treatment with tienilic acid was then begun according to the following regimen:

Days 1, 2, 3	125 mg 8 am
Days 4, 5, 6	125 mg 8 am and 4 pm (125 mg b.i.d.)
Days 7, 8, 9	250 mg 8 am
Days 10, 11, 12	250 mg 8 am and 4 pm (250 mg b.i.d.)
Days 13, 14, 15	500 mg 8 am

Indomethacin was given as required for treatment of acute gout, but was not prescribed prophylactically. All patients gave informed consent.

Results

PLASMA URIC ACID

Changes produced by different dosage regimens can

be seen in Tables 1 and 2 and Fig. 1. In Table 1 levels have been measured at 8 am each day prior to any medication that day. In Table 2 samples have been drawn at 8 am, noon, 4 pm, 8 pm, and 12 midnight on the third day of each dosage regimen, and then at 8 am the following morning, before each regimen alteration. The levels at the times when dosage regimens change (that is, 8 am on days 4, 7, 10, and 13) are plotted in Fig. 1, expressed as the percentage alterations from the pretreatment level. Statistical comparisons at these change-over points are shown in Table 3.

URINARY URIC ACID

Table 4 shows average uric acid excretion for each 3-day dosage regimen, while in Fig. 2 the excretion in each 4-hourly period has been averaged for the 4 patients (a total of 12 values over the 3 days of each dosage regimen), and plotted cumulatively to show the excretion rate through 24 hours.

Table 1 Mean plasma uric acid (8 am)

Day	Tienilic acid dose (mg)		Plasma uric acid ($\mu\text{mol/l}$)
	8 am	4 pm	
1	125	Nil	516
2	125	Nil	492
3	125	Nil	486
4	125	125	474
5	125	125	372
6	125	125	318
7	250	Nil	348
8	250	Nil	348
9	250	Nil	354
10	250	250	336
11	250	250	264
12	250	250	246
13	500	Nil	240
14	500	Nil	270
15	500	Nil	282
16	Discharge	—	306

URATE CLEARANCE

Since the serum uric acid fluctuated considerably over each 3-day dosage regimen, the clearance was calculated in each case by averaging the 5 samples

Table 2 Mean plasma uric acid: diurnal variation with tienilic acid ($\mu\text{mol/l}$)

Dosage regimen	0800 8 am	1200 Noon	1600 4 pm	2000 8 pm	2400 Mid- night	0800 8 am
125 mg 8 am	486	414	402	396	408	474
125 mg 8 am, 4 pm	318	312	288	258	258	348
250 mg 8 am	354	306	282	264	270	336
250 mg 8 am, 4 pm	246	210	216	204	204	240
500 mg 8 am	282	252	234	252	282	306

Table 3 Tienilic acid: statistical comparison* of different regimens

Regimens compared		Decrease in plasma uric acid	Increase in urinary uric acid	Increase in clearance uric acid
125 mg am Nil	NS		NS	NS
125 mg b.i.d. Nil	<0.001		<0.001	<0.005
250 mg am Nil	<0.05		<0.01	<0.05
250 mg b.i.d. Nil	<0.001		<0.01	<0.005
500 mg am Nil	<0.005		<0.05	<0.05
125 mg b.i.d. 125 mg am	<0.0005		<0.005	<0.0005
125 mg b.i.d. 250 mg am	NS		<0.005	<0.05
250 mg b.i.d. 250 mg am	<0.0005		<0.05	<0.0005
250 mg b.i.d. 125 mg b.i.d.	<0.05		NS	<0.001
250 mg b.i.d. 500 mg am	<0.05		<0.05	<0.05

*P values.

Table 4 Urinary uric acid (mmol/24 hours)

Patient	Nil	125 mg am	125 mg b.i.d.	250 mg am	250 mg b.i.d.	500 mg am
1	4.0	3.6	5.4	4.5	6.2	4.4
2	3.1	4.3	5.2	4.6	6.3	4.4
3	3.7	5.7	6.0	4.5	7.0	6.2
4	2.3	3.8	3.9	3.1	3.4	3.0
Average	3.3	4.3	5.1	4.2	5.7	4.5

Fig. 1 Percentage alteration in plasma uric acid level at times of alteration in dosage regimen.

Fig. 2 Urinary uric acid measured 4-hourly, and plotted cumulatively to show excretion rates through 24 hours.

Fig. 3 Uric acid clearance, calculated on the third day of each dosage regimen.

taken on the final 24 hours of each treatment period (noon, 4 pm, 8 pm, 12 midnight, 8 am), and by using the 24-hour urine excretion on this 3rd day only. The results are shown in Fig. 3.

BLOOD PRESSURE

While values at 6 am were generally a little lower than those later in the day, it was felt that the 10 am reading more closely represented the average throughout the 24-hour period and would also allow more satisfactory follow-up after discharge, in that patients would attend the outpatient clinic at about this time of day. As can be seen from Fig. 4, reduction in systolic and diastolic pressures (resting) was seen with all dosage regimens, though the greatest average reduction was found with 250 mg b.i.d. (158/104 to 139/91).

FLUID BALANCE/URINARY ELECTROLYTES

Fig. 5 shows the average fluid balance for the 4 patients for each day of treatment. Although a diuresis was evident with all treatment schedules, there appears a trend towards a more vigorous diuresis with the 250 mg b.i.d. regimen. The same trend appears with 24-hour urinary potassium, but no obvious pattern appeared with urinary sodium.

SIDE EFFECTS

Hypokalaemia. Table 5 shows serum potassium levels before treatment and before discharge from hospital, this difference being significant ($P < 0.05$).

Serum creatinine. Serum creatinine rose on average

Fig. 4 Average blood pressure measurements at 10 am for each dosage regimen.

Fig. 5 Daily fluid balance measurements, expressed as average net gain or loss for each dosage regimen.

Table 5 Tienilic acid: serum potassium, renal function

Patient	Serum potassium (mmol/l)		Serum creatinine (μ mol/l)		Creatinine clearance (ml/min)	
	Pre-treatment	Post-Treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
1	3.0	2.9	119	159	120	54
2	3.9	3.6	107	88	83	105
3	3.7	3.0	78	181	90	47
4	3.7	3.1	103	131	101	74
Average	3.6	3.1	103	131	101	74

Fig. 6 Alteration in plasma urate with different dosage regimens, to show time of appearance of acute gout (patient 1 in Tables 4 and 5).

by 28 $\mu\text{mol/l}$ throughout the admission, and creatinine clearance fell by 27 ml/min. There was, however, considerable variation among the 4 patients, and these differences did not reach statistical significance.

Acute gout. Acute attacks were seen in 3 of the 4 patients and required treatment with indomethacin. In 2 of these the onset appeared during a single daily dosage regimen. Fig. 6 illustrates the more striking example.

Discussion

These results with tienilic acid indicate the possibility of controlling hyperuricaemia, gout, and hypertension with a single agent. Although the number of patients was small, statistically significant reductions in serum uric acid and increased urinary uric acid excretion were consistently obtained. While there was an alteration from pretreatment values with single daily dosage, the urinary urate excretion was not increased with increased single morning dosage, even from 125 mg to 500 mg. The serum uric acid levels are a little more difficult to compare in that the baseline level before each dosage regimen varied according to the effect achieved with the previous regimen. Best results were obtained with 250 mg b.i.d. with the greatest plasma uric acid reduction and increase in urate clearance.

The reductions in systolic and diastolic blood pressure are of a similar order to those previously reported with thiazide diuretics.¹⁰ Trials comparing tienilic acid and various thiazides found no significant difference between the various agents.^{11, 12}

Side effects seen were those one might theoretically

expect with an agent of this type. In common with the thiazides the drug reduces serum potassium, and 1 patient required potassium supplements. Serum creatinine levels varied considerably from patient to patient, with a trend towards an increase during hospital admission, associated with a fall in creatinine clearance. These values did, however, tend to revert to the pretreatment stage over the months following discharge while the patients continued to take the drug. Approximately 3 months after discharge, 1 patient, a severe overproducer of uric acid previously intolerant of other urate-lowering medications, including allopurinol, developed left iliac fossa discomfort with strangury, and was presumed to have passed a small calculus. The intravenous pyelogram at the time was completely normal.

Acute gout developed in 2 of the 4 patients, while a third, the overproducer mentioned above, had moderately severe gout attacks before as well as during treatment. These attacks tended to be associated with the greater diurnal fluctuations in serum urate produced by the single daily dose regimen. Their development is similar to the appearance of acute attacks in the initial periods after starting treatment with probenecid, allopurinol, or other urate-lowering drugs.¹³⁻¹⁵

The short duration of this study and the small numbers involved make it impossible to state that the drug will ultimately prevent further attacks of gout, but serum urate levels in all 4 patients have remained remarkably consistent over the months following discharge. In comparison with the average pretreatment level of 8.6 mg per 100 ml (516 $\mu\text{mol/l}$), the average level was 4.0 mg per 100 ml (240

μmol/l) 3 months after discharge, on 250 mg twice daily in 3 patients and 500 mg twice daily in 1 (no dietary restriction).

The following conclusions may be drawn. Tienilic acid is an effective uricosuric agent in patients with gout; the magnitude of this effect is considerably greater in a twice daily than a single daily dosage. Raised serum uric acid levels in patients with gout were reduced to normal, with an average reduction of 50% from the pretreatment value with 250 mg twice daily. Similar antihypertensive action was seen with all dosages used. The development of acute gout attacks appeared to reflect fluctuating serum uric acid levels, seen more with single daily dosage. Tienilic acid offers the potential for control of commonly associated hyperuricaemia, gout, and hypertension with a single agent.

ADDENDUM: During the course of publication tienilic acid was withdrawn from further use in the United States, where it had been freely available on prescription, because of reports of hepatotoxicity. It has also been withdrawn from clinical trials in Great Britain, although it continues to be prescribed on the Continent. No abnormalities of liver function tests were seen in this study.

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