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Allopurinol treatment and its effect on renal function in gout: a controlled study

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SUMMARY Fifty-nine patients with primary gout were treated with either a combination of colchicine and allopurinol or colchicine alone. Assessments of renal function over 2 years revealed a statistically significant fall of glomerular filtration rate and urine concentrating ability in those receiving only colchicine. The renal function of patients given allopurinol did not change. Treatment with allopurinol resulted in a significant reduction of ammonium excretion, a phenomenon which could not be readily explained. Urate clearance also declined during allopurinol treatment, and the impaired urate clearance associated with gout became more evident. The most important observation was that allopurinol retarded an apparent decline of renal function. Presumably this was achieved through its hypouricaemic effect and implies that the hyperuricaemia of gouty patients is deleterious to the kidneys.

It is surprising that a disease with as venerable a history as gout should provoke controversy, and yet it is still argued whether gout may cause renal impairment. In recent articles it has been claimed that kidney disease remains the most frequent complication of gout and that it is less likely to develop in those patients given adequate treatment.[1 2] On the other hand it has also been reported that untreated patients are no more likely to develop renal impairment than those receiving hypouricaemic therapy.[3] Furthermore, in the experience of Yu *et al.*[4] deterioration of renal function in gout occurs rarely and when it arises can be attributed to hypertension, diabetes, arteriosclerosis, or unrelated kidney disease.

In a previous study we noted that a population of untreated gouty patients had reduced glomerular and tubular function compared with age-matched controls.[5] Severe renal impairment was not a feature, and the observations were consistent with a slowly progressive disturbance of kidney function. The relative insufficiency of the gouty kidneys could not be attributed to stone formation, urinary infection, hyperuricosuria, alcohol excess, or, with some exceptions, to hypertension. Weinman,[6] in summarising the extensive literature, concluded that, although the evidence was incomplete, hyperuricaemia itself seemed the most likely cause of kidney damage. If this were true, one might anticipate that hypouricaemic treatment would prevent kidney dysfunction in gout. There have been remarkably few attempts to answer this question.

No consistent effect of allopurinol on renal function was observed in gout patients with kidney failure[7] nor on that of hyperuricaemic patients with various renal diseases in the absence of gout.[8] Improvements of glomerular function have been noted in a small number of gout patients during allopurinol treatment, but these may have been due to the eradication of renal calculi.[9] Scott[10] has noted that in our present state of knowledge it is impossible to say whether lowering blood uric acid in asymptomatic hyperuricaemic subjects lessens the risk to the kidneys. This statement is equally pertinent to gout, where the degree of hyperuricaemia may be more pronounced.

We have attempted to determine whether allopurinol therapy may influence the progression of renal insufficiency in gout by comparing the kidney function of gouty patients treated with colchicine alone with that of patients receiving both colchicine and allopurinol. Our preliminary findings suggested that after 1 year a decline of urine concentrating ability was apparent among those treated with only colchicine but was not seen in those given allopurinol as well.[11] The present report documents our expanded observations in a larger number of patients over a period of 2 years.

Patients and methods

Fifty-nine patients were admitted to the study. All had experienced at least 1 attack of acute arthritis

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associated with a raised blood uric acid unrelated to drugs or other diseases. None was receiving regular hypouricaemic treatment, though many had undergone sporadic treatment in the past. Thirteen patients had mild hypertension (supine diastolic blood pressure >100 mgHg), which was treated throughout with nondiuretic hypotensive agents. Two had histories of renal calculi, but none had overt evidence of other kidney disorders.

During the period of initial investigation patients received colchicine 0·5 mg twice daily. Their height, body weight, and supine blood pressure were measured and urine samples were obtained after 15 hours' fluid deprivation for osmolality estimation. Measurement of ^{51}Cr-edetic acid clearances was used to assess glomerular filtration rates (GFR).[12] Blood samples were obtained for urea and creatinine which were estimated by standard Auto Analyzer techniques. Fasting serum triglyceride and cholesterol were measured by the respective methods of Wahlefeld[13] and Searcy and Bergquist.[14] On the last day of a 4-day, low-purine, and a alcohol-free diet, 24 h urine collections were obtained. Each voided sample was collected separately under toluene and paraffin for pH estimation and then pooled. Urine excretion of protein was measured by the biuret reaction and ammonium and titratable acid by the method of Chan.[15] Uric acid levels of the urine and of blood obtained on completion of the urine collections were measured by the method of Simmonds.[16] This uricase technique provides values which are approximately 25% lower than those achieved by the uricase method adapted to the AutoAnalyzer.

Patients were randomly allocated to 2 treatment groups which were stratified for age (less than or more than 50) and the presence or absence of hypertension. One group was treated with colchicine 0·5 mg twice daily and the other with allopurinol 200 mg daily in addition to colchicine. All obese patients were advised to lose weight, and those who drank excessive amounts of alcohol were urged to limit their intake. One patient was withdrawn from the randomisation schedule and given allopurinol because he had large tophi.

At 2- or 3-month intervals patients were reviewed, and body weight, blood pressure, plasma uric acid, urea, and creatinine were estimated. Attacks of gout were noted. All patients were followed up for at least 1 year, and 55 were assessed over 2 years. The full range of investigations was repeated after 1 and 2 years of treatment. Allopurinol compliance was monitored by following serial blood uric acid levels. Three patients failed to take allopurinol regularly and were reallocated to the colchicine treatment group for the purposes of analysis.

For various reasons it was not possible to perform all investigations for every patient at each annual assessment. It was therefore considered appropriate to analyse only those results which could be paired with a previous or subsequent investigation for analysis by Student's *t* test. Other statistical methods employed were the *t* test for independent data and the chi-square test.

Results

The essential clinical characteristics of the patients who entered the study are seen in Table 1. The treatment groups were well matched with regard to age, prevalence of hypertension, and renal stones, but a family history of gout was significantly more frequent among the allopurinol treated patients.

In the first year of treatment 10 (30%) of the colchicine group had recurrent attacks of gout compared with 5 (19%) of the allopurinol patients ($\chi^2 = 0{\cdot}94$, NS). Mean body weights did not alter over 2 years, though individuals registered gains and reductions of weight over this period. No new examples of hypertension occurred, and no patient with established hypertension had a recorded diastolic blood pressure in excess of 110 mgHg. No significant alterations of mean fasting serum lipids was observed over 2 years, but serum cholesterol did decline slightly in the allopurinol treated group from a mean (± SD) of 6·8 (± 1·2) to 6·2 (± 1·3) mmol/l (263 ± 46 to 240 ± 50 mg/100 ml) ($t = 1{\cdot}34$, NS).

The sequential results of mean renal function tests are outlined in Table 2. In neither treatment group was there a significant alteration of blood urea or creatinine. The mean GFR of the colchicine group declined significantly after 1 year and to a lesser extent between the first and second years. This was

Table 1 *Main clinical characteristics of the 2 treatment groups*

Treatment schedule	*Colchicine alone*	*Colchicine with allopurinol*
No. of patients	33	26
Sex	33 M	25 M 1 F
Mean age ± SD	49±12	49±12
Mean body weight ± SD (kg)	80±9·6	83±14·0
Family history of gout	6 (18%)	12 (46%)*
Hypertension	6 (18%)	7 (27%)
Regular alcohol (>2 pints beer/day)	23 (69%)	18 (69%)
Mean duration of gout ±SD (yr)	5·4±5·9	6·4±6·0
Tophi	7 (21%)	3 (11%)
Renal calculi	1 (3%)	1 (4%)
Initial GFR ±SD (ml/min/1·73 m²)	98±17	90±24†
Initial urine conc. ± SD (mosm/kg)	830±106	791±148‡

*$\chi^2 = 5{\cdot}36$; $p < 0{\cdot}025$. †$t = 1{\cdot}58$; NS. ‡$t = 1{\cdot}12$; NS.

Table 2 *Mean ± SD of renal function tests in the 2 treatment groups over 2 years. The figures represent only those results which could be paired with previous or subsequent values*

	Treatment schedule	*Time period*			*No. paired observations*	t	*p*
		0	*1 yr*	*2 yr*			
Blood urea (mmol/l)	Colchicine	6·2±1·6	—	6·2±1·6	30	0·05	NS
	Allopurinol	6·6±1·6	—	6·3±1·1	22	0·97	NS
Blood Creatinine (μmol/l)	Colchicine	97±17	—	92±17	29	1·47	NS
	Allopurinol	97±19	—	93±16	21	1·03	NS
GFR (ml/min/1·73 m²)	Colchicine	98±17	93±15	—	33	2·5	<0·02
		98±17	—	91±16	32	2·47	<0·02
	Allopurinol	91±23	93±24	—	25	0·68	NS
		87±24	—	89±24	22	0·77	NS
Urine conc. ability (mosm/kg)	Colchicine	822±106	789±135	—	29	2·21	<0·05
		835±109	—	770±138	29	3·95	<0·001
	Allopurinol	792±154	798±144	—	22	0·23	NS
		772±147	—	772±149	20	0·02	NS
No. with >0·1g/24 h proteinuria and quantity of proteinuria (g/24 h)	Colchicine	9	—	10	—	—	—
		(0·23±0·14)		(0·34±0·45)			
	Allopurinol	8	—	8	—	—	—
		(0·86±1·3)		(0·76±1·1)			

Conversion SI to traditional units: urea × 6·0; creatinine × 0·0113.

paralleled by a significant reduction of urine osmolality. By contrast, those patients receiving allopurinol exhibited no significant deterioration of either of these measurements. Their mean GFR actually increased slightly. The frequency and mean quantity of proteinuria of both treatment groups did not alter significantly.

Of those who completed 2 years of treatment 12 (37%) of the colchicine-only patients had diminutions of GFR in excess of 10 ml/min/1·73 m². Only two (9%) of the allopurinol treated patients had deteriorations of this magnitude ($\chi^2 = 5{\cdot}76$, $p < 0{\cdot}025$). The features of the 12 with >10 ml/min/1·73 m² reductions of GFR were compared with those colchicine only patients who had lesser changes (Table 3). There was no obvious disparity between these 2 groups, and, in particular, the frequency of hypertension, tophi, and regular alcohol consumption was similar. There were no significant differences between the initial mean values of blood uric acid, urate excretion, and urine concentrating ability.

The diurnal pattern of urine pH did not change, and the characteristic and persistently acid urine of both groups of gout patients was sustained over 2 years. The minimum, maximum, and range of urine pH values throughout the day and the mean pH of the pooled 24 h collections, did not alter significantly with either treatment schedule (Table 4). Net acid excretion fell, but not significantly, in both treatment groups after 2 years. Among those who received

Table 3 *A comparison of colchicine treated patients whose GFR declined more than 10 ml/min/1·73 m² with those whose GFR did not. The figures represent means ± SD*

	Reduction GFR>10 ml/min	*Little change of GFR*	t	*p*
No. patients	12	20	—	—
Age ± SD	46±14	50±10	0·85	NS
Body wt ± SD (kg)	80±7·0	82±10·7	0·57	NS
Family history of gout	2 (17%)	3 (15%)	—	—
Regular alcohol	10 (83%)	12 (60%)	$\chi^2=1{\cdot}66$	NS
Tophi	3 (25%)	3 (15%)	—	—
Pretreatment plasma uric acid ± SD (mmol/l)	0·37±0·1	0·38±0·1	0·39	NS
Pretreatment uric acid excretion ± SD (mmol/24 h)	3·3±1·1	3·1±0·9	0·63	NS
Initial urine conc. ± SD (mosm/kg)	833±84	832±113	0·01	NS

Conversion SI to traditional units: plasma uric acid × 16·8; urine uric acid × 168.

colchicine alone there were no significant changes of either ammonium or titratable acid excretion. Allopurinol was associated with a statistically decline of ammonium output, but titratable acid excretion was unaltered. The mean ammonium excretion in the allopurinol treated group was initially higher, but this does not explain the observed fall of excretion.

As anticipated, plasma and urine uric acid levels declined significantly during allopurinol treatment

Table 4 *The mean pattern of urine pH and mean ± SD 24 h urine pH and hydrogen ion excretion in the 2 treatment groups over 2 years*

	Treatment schedule	*Time period*			*No. paired observations*	t	*p*
		0	*1 yr*	*2 yr*			
Daily minimum-maximum	Colchicine	5·3–6·3	—	5·3–6·3	—	—	—
	Allopurinol	5·1–5·9	—	5·0–5·8	—	—	—
pH 24 h urine	Colchicine	5·7±0·4	—	5·8±0·4	20	0·12	NS
	Allopurinol	5·4±0·4	—	5·3±0·3	17	1·15	NS
Ammonium excretion (mmol/24 h)	Colchicine	33±12	31±9	—	22	0·65	NS
		33±12	—	30±9	21	1·2	NS
	Allopurinol	40±13	30±14	—	17	3·05	<0·01
		38±11	—	31±10	17	2·28	<0·05
Titratable acid excretion (mmol/24 h)	Colchicine	22±11	20±9	—	22	0·89	NS
		22±11	—	19±8	21	0·94	NS
	Allopurinol	23±12	20±13	—	16	0·63	NS
		23±11	—	23±7	18	0·06	NS
Net acid excretion (mmol ± SD)	Colchicine	55±22	—	49±13	21	1·22	NS
	Allopurinol	61±16	—	54±14	17	1·88	NS

Table 5 *Mean ± SD plasma and urine uric acid, with uric acid clearance values of both treatment groups*

	Treatment schedule	*Time period*		*No. paired observations*	t	*p*
		0	*2 yr*			
Plasma uric acid (mmol/l)	Colchicine	0·38±0·06	0·37±0·1	31	0·56	NS
	Allopurinol	0·4±0·07	0·28±0·07	21	6·7	<0·001
Uric acid excretion (mmol/24 h)	Colchicine	3·2±0·1	2·9±0·9	25	1·29	NS
	Allopurinol	3·1±1·1	1·9±0·8	21	8·82	<0·001
Urate clearance (ml/min/1·73 m²)	Colchicine	5·3±1·7	4·6±1·1	24	1·94	NS
	Allopurinol	4·8±1·4	3·8±1·3	21	4·01	<0·001
$\frac{Cur}{GFR} \times 100$ (%)	Colchicine	5·5±1·9	5·2±1·5	24	0·63	NS
	Allopurinol	5·8±1·74	4·4±1·4	21	4·0	<0·001

Cur = urate clearance. GFR = glomerular filtration rate.

(Table 5). Urate clearance fell in both treatment groups, although by the second year the trend was significant only for those receiving allopurinol. When urate clearance was expressed as a percentage of GFR, the decline of clearance was less evident in the colchicine group but remained significant for those given allopurinol.

Discussion

The 2 treatment groups were evenly matched and no patient developed worsening of hypertension, a feature which is common in gout and which may contribute to renal impairment.[17] It is thus very likely that the choice of treatments influenced the striking differences which were observed in the sequential measurements of renal function. The possibility that colchicine might have an adverse effect on the kidneys was met by ensuring that all patients received this drug. As anticipated, those subjects given allopurinol experienced fewer episodes of gouty arthritis, although the frequency of attacks was not significantly different between the treatment groups. Colchicine is an effective inhibitor of acute gout.[18 19]

Incidental to the studies of renal function were recordings of fasting serum lipids. We have previously suggested that allopurinol may reduce serum cholesterol after 4 weeks of treatment.[20] The current observations failed to demonstrate a significant effect of allopurinol on cholesterol after 2 years, although a slight fall was apparent. This implies that the original observations were erroneous or reflected a transient effect.

Neither treatment was associated with alterations of blood urea or creatinine, but a decline of the

more sensitive indices of renal function was seen in those patients given colchicine alone. This was more pronounced in the first year of the study. These changes contrasted with the lack of deterioration in the mean values of the allopurinol group.

The colchicine treated patients who showed the greatest reduction of GFR over 2 years were not distinguished by any predictive clinical or laboratory features. They did not have initially worse renal concentrating ability, a deficiency which has been considered the first indication of gouty nephropathy.[21]

Although the differences noted were statistically significant their clinical significance could be questioned.

If the mean GFR of those given only colchicine were to continue declining at the rate observed in the first year, the figure projected over 10 years would come to represent that of severe renal insufficiency. This would seem unlikely. Profound disturbance of kidney function was not apparent in our earlier study of gouty patients, even among those with a long history.[5] This may have reflected the deficiencies of a horizontal study and may imply that those patients who develop renal failure are unlikely to come to a rheumatology clinic in the first instance. Grahame and Scott[22] did note a raised blood urea in 25% of their large series of gouty patients, but concluded that in general there was little deterioration of renal function with time. Gout is at present a rare cause of terminal kidney disease and accounts for very few of those requiring dialysis or transplantation.[23] It is possible that the widespread use of hypouricaemic agents has had a substantial impact on the prevalence of severe renal insufficiency.

The decline of mean GFR of the colchicine treated group was slight in the second year of the study, suggesting that the natural rate of deterioration may be on average much less than that observed in the first year. The mean decrement was mainly attributable to a greater fall of GFR in approximately one-third of the group taking colchicine. It was not possible to say whether there were patients among these whose kidneys dysfunction would have continued to decline rapidly or whether their renal impairment would have proceeded at a variable or intermittent pace. Why the reduction of GFR was greater in some patients than others was also not clear.

The most important observation of this study is that allopurinol treatment can retard an apparent decline of renal function in gout. Presumably this is achieved by its hypouricaemic effect and supports the contention that hyperuricaemia is by itself deleterious to the kidney. The data refer specifically to gouty patients and do not necessarily imply that asymptomatic hyperuricaemia exerts a similar effect. It was not possible to define a critical level of hyperuricaemia above which renal impairment progressed. Indeed, those patients who registered most decline of GFR did not have higher blood uric acid levels at the outset of the study. However, it is possible that given the day-to-day fluctuations of blood uric acid, especially in relation to diet and alcohol, unrecorded differences in the degree of hyperuricaemia may have occurred. The mechanism by which hyperuricaemia may induce renal dysfunction in gout was formerly never in question. Necropsy studies conducted 2 or 3 decades ago regularly showed urate crystal deposition within the renal parenchyma.[24–26] Studies in animal models have suggested that acute intratubular uric acid deposition may be a primary event.[27] Other recent studies of renal histopathology in gouty men have revealed urate crystals in only a small percentage of cases[28] or none at all.[29] Neither of the latter studies attempted to determine whether hypouricaemic treatment might have influenced the findings. Our results are consistent with the view that, in some patients with gout, urate crystals are precipitated within the kidney and impair its function. This concept has been recently dismissed as a debatable entity,[4] though other workers have continued to assert that it is an important mechanism of renal disease in gout.[30 31]

Measurements of urine pH in both treatment groups showed no alteration of the diurnal rhythm, which in gout tends to fluctuate normally but at much lower pH values.[5] Disturbances of the daily pattern of urine pH have been considered early evidence of renal involvement.[32] The lack of change in the colchicine treated patients, despite the deterioration of GFR and urine concentrating ability, suggests that aberrations of acid excretion in gout may not be linked with renal function. In both treatment groups there was no change of the mean 24 h urine pH nor of titratable acid excretion, but ammonium excretion declined significantly in those given allopurinol. In a previous study allopurinol did not appear to have any effect on ammonium excretion when gout patients were given an acid load.[33] Our own investigations have confirmed that the low urine pH of gouty subjects is associated with excretion of more titratable acid and proportionally less ammonium than controls, a phenomenon which cannot be attributed to renal dysfunction.[5]

The relationship between uric acid and ammonium metabolism in gout has been ascribed by Gutman and Yu[34] to a preferential utilisation of glutamine for uric acid synthesis and a resultant deficiency of ammonia production. Studies conducted by us and others have demonstrated a reciprocal relationship between uric acid and ammonium excretion when patients have

been subjected to an acid load.[35 36] This provides further evidence for a close metabolic relationship between uric acid and ammonium, but it is difficult to reconcile the hypothesis of Gutman and Yu[34] with the reduction of both ammonium and uric acid excretion which followed allopurinol treatment in the present study. Taken together the various observations of hydrogen ion excretion in gout are difficult to explain on the basis of accepted metabolic pathways.

During the 2 years of the study mean urate clearance declined in both treatment groups but to a significant extent only among those given allopurinol. When corrected for GFR the urate clearance of the colchicine treated patients more closely approximated the pretreatment level, and the observed fall was most likely a function of renal deterioration. The generally low urate clearance of gouty patients can only be partly attributed to loss of functioning nephrons.[5] The reduction of urate clearance remained significant among the allopurinol treated group even when corrected for GFR. Thus urate clearance was responsive to a fall of blood uric acid levels in just the same way as clearance in healthy subjects may be modulated by a decrease of circulating uric acid.[37] A similar response to allopurinol was recorded by Gutman *et al.*,[38] who also noted a rise of urate clearance in gouty patients given RNA dietary supplements. They concluded that the data indicated a normal pattern of urate clearance in gout. However, the clearance of their patients was consistently less than that of controls with equivalent blood uric acid levels. In a critical evaluation of several classical papers, including that of Gutman *et al.*,[38] Simkin[39] showed that for any given blood uric acid level the average gouty individual excretes substantially less uric acid. The weight of evidence thus favours the existence of a quantitative defect of urate clearance which is independent of other aspects of renal function and which probably contributes to the initial development of hyperuricaemia.

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