

Efficacy and Tolerability of Probenecid as Urate-lowering Therapy in Gout; Clinical Experience in High-prevalence Population

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ABSTRACT. Objective. Probenecid is recommended as urate-lowering therapy (ULT) in patients with gout where xanthine oxidase inhibitors are ineffective, not tolerated, or contraindicated. The aim of our study was to determine the efficacy of probenecid to achieve serum urate (SU) targets (< 0.36 mmol/l) in clinical practice.

Methods. We identified 57 patients prescribed with probenecid from a database of 521 rheumatology clinic attenders with gout. Demographic characteristics, indications for probenecid, probenecid doses, side effects, and laboratory data including estimated glomerular filtration rate (eGFR) and SU were recorded.

Results. There were 30/57 (53%) patients treated with probenecid as monotherapy and 27/57 (47%) patients treated with probenecid in combination with allopurinol. Target SU concentrations (< 0.36 mmol/l) were achieved in 10/30 (33%) of the probenecid monotherapy group and 10/27 (37%) of the combination treatment group. Baseline SU concentrations, but not eGFR or probenecid dose, independently predicted achievement of target SU. Target SU was achieved in 5/15 (33%) patients with eGFR < 50 ml/min/1.73 m². There was no difference in the percentage of patients achieving SU target in those with eGFR < 50 ml/min/1.73 m² compared with those with eGFR ≥ 50 ml/min/1.73 m². Adverse events attributed to probenecid were observed in 8/42 (19%) patients with eGFR ≥ 50 ml/min/1.73 m² and in 2/15 (13%) patients with eGFR < 50 ml/min/1.73 m².

Conclusion. Probenecid has moderate efficacy as ULT in clinical management of patients with complex gout who have a lack of efficacy or intolerance to allopurinol. Patients with chronic kidney disease may respond to probenecid with similar rates of adverse events. (J Rheumatol First Release March 1 2013; doi:10.3899/jrheum.121301)

Key Indexing Terms:

GOUT

PROBENECID

URATE

TARGET

Probenecid was introduced more than 60 years ago as urate-lowering therapy (ULT) for gout^{1,2,3,4,5}. This drug is a uricosuric agent that inhibits active renal reabsorption of uric acid through various urate transporters in the proximal tubular epithelial cells^{6,7,8}. Despite its effectiveness, probenecid is rarely used in clinical practice worldwide⁹. Potential barriers to probenecid use are the availability of other ULT agents such as allopurinol, the requirement of multiple daily dosing, potential side effects including nephrolithiasis, and the apparent lack of efficacy in gout patients with chronic kidney disease^{4,10,11}.

The 2012 American College of Rheumatology (ACR)

gout management guidelines have highlighted the importance of achieving a target serum urate (SU) < 0.36 mmol/l (6 mg/dl) for longterm effective treatment of gout¹². These guidelines recommend probenecid as alternative first-line ULT in patients who have failed xanthine oxidase inhibitor (XOI) therapy owing to contraindications or intolerance. Both monotherapy and combination therapy with XOI drugs are recommended as treatment options within the guidelines. The 2006 European League Against Rheumatism recommendations for gout management included probenecid as an alternative to allopurinol in patients with normal renal function, and stated that this drug should not be used in patients with renal impairment because of lack of efficacy¹³.

New Zealand has high prevalence of gout, particularly in Maori and Pacific people^{14,15}. Contemporary gout prevalence in New Zealand adults is estimated to be 3.2% in Europeans, 6.1% in Maori, and 7.6% in Pacific people¹⁵. As with many other countries, studies from New Zealand have demonstrated low achievement of SU targets in patients receiving allopurinol monotherapy¹⁶. Current ULT options in New Zealand are allopurinol, probenecid, and off-label benzbromarone^{16,17}. Given these limited treatment options,

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the high prevalence of disease, and the growing recognition of the importance of SU targets for effective gout management, probenecid use is increasing in New Zealand. Our aim was to determine the efficacy of probenecid to achieve SU targets in the management of gout in daily clinical practice.

MATERIALS AND METHODS

This was a retrospective observational study of patients attending rheumatology outpatient clinics for management of gout in Central and South Auckland, New Zealand. In these clinics, urinary uric acid is not routinely measured prior to starting uricosuric therapy because the majority of our patients have hyperuricemia on the basis of uric acid underexcretion¹⁸. At the time of commencing uricosuric therapy, all patients are advised to maintain excellent fluid intake (at least 2 l of water per day). Urine alkalinization is not routinely prescribed.

Patients included in the analysis had a diagnosis of gout based on the ACR classification criteria¹⁹ and were prescribed probenecid on at least 1 occasion between January 2008 and December 2010. These patients were identified from a database of 521 clinic attendees. Details regarding demographic characteristics, medical history, indications for probenecid, probenecid doses, side effects of treatment, and laboratory data were collected from an electronic records system that included inpatient discharge summaries, outpatient clinical records, and all hospital and community blood test results. Where probenecid dose was increased, the maximum dose was used in the analysis. Posttreatment SU was defined as the SU concentration following at least 1 month of maximum probenecid treatment. The mean period between commencing maximum probenecid treatment and posttreatment SU was 3.0 (SD 0.9) months. Patients were included in the analysis only if pre- and posttreatment SU measurements were available. Target SU concentrations were defined as <0.36 mmol/l (6 mg/dl). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation²⁰. The local ethics committee approved our study.

Data were analyzed using SPSS version 13 (SPSS Inc.) and Prism version 5 (GraphPad). Student t tests were used to determine the differences between means. Repeated measures ANOVA was used to compare differences in the allopurinol-probenecid combination group, with Tukey posthoc tests to determine differences between groups. Logistic regression analysis was used to determine the predictors of achieving target SU concentrations following probenecid treatment. P values are expressed as 2-tailed values. Unless otherwise specified, data are expressed as mean (SD).

RESULTS

Patient characteristics. From the database of 521 eligible clinic attendees, we identified 57 patients (10.9%) for analysis. There were 30/57 patients (53%) treated with probenecid as monotherapy (monotherapy group) and 27/57 patients (47%) treated with probenecid in combination with allopurinol (combination therapy group). Probenecid monotherapy was used in 3 patients in whom allopurinol was relatively contraindicated because of concomitant azathioprine use. For the remaining 27 patients, probenecid monotherapy was prescribed because of allopurinol intolerance. All patients in the combination therapy group were started on probenecid because of inadequate control of SU concentrations with allopurinol monotherapy. Two patients had a history of kidney stones.

The clinical characteristics and medication doses of all patients treated with probenecid, the monotherapy group,

and the combination therapy group are shown in Table 1. The mean dose of probenecid was 1.29 (SD 0.68) g/day in the monotherapy group and 0.99 (SD 0.44) g/day in the combination group. The maximum allopurinol dose in the combination therapy group was 600 mg daily. Patients receiving probenecid monotherapy were more likely to be female than those in the combination therapy group. Baseline SU concentrations (prior to starting any ULT) were higher in the combination therapy group, compared with the monotherapy group.

SU concentrations in probenecid-treated patients. Target SU concentrations (<0.36 mmol/l) were achieved in 10/30 (33%) of the probenecid monotherapy group and 10/27 (37%) of the combination treatment group. Both monotherapy and combination therapy with probenecid led to a significant reduction in SU concentrations (Table 2). In the monotherapy group, mean SU concentrations diminished from 0.58 (SD 0.09) mmol/l to 0.41 (SD 0.09) mmol/l ($p < 0.0001$). In the combination therapy group, mean SU concentrations diminished from baseline values of 0.63 (SD 0.09) mmol/l to 0.50 (SD 0.11) mmol/l on allopurinol monotherapy, and to 0.38 (SD 0.10) mmol/l on combination therapy (ANOVA $p < 0.0001$; Tukey posthoc test baseline vs allopurinol monotherapy $p < 0.001$; Tukey posthoc test allopurinol monotherapy vs combination therapy $p < 0.001$). Combination therapy was associated with greater change in SU from baseline compared with monotherapy (Table 2).

Predictors of target SU in probenecid-treated patients. Probenecid doses were similar between patients who

Table 1. Clinical characteristics

Characteristic	All, n = 57	Probenecid Monotherapy, n = 30	Combination Therapy, n = 27	p*
Age, yrs, mean (SD)	57 (16)	59 (17)	54 (14)	0.23
Male, n (%)	44 (77)	17 (57)	27 (100)	<0.001
Ethnicity, n (%)				
Maori or Pacific	31 (54)	15 (50)	16 (59)	0.48
Non-Polynesian	26 (46)	15 (50)	11 (40)	
Tophaceous gout, n (%)	34 (60)	16 (53)	18 (67)	0.31
Serum creatinine, μ mol/l, mean (SD)	114 (32)	110 (33)	117 (31)	0.41
eGFR, ml/min/1.73 m ² , mean (SD)	61.0 (20.2)	59.7 (19.6)	62.4 (21.1)	0.61
Baseline serum urate, mmol/l**	0.60 (0.09)	0.58 (0.09)	0.63 (0.09)	0.041
Allopurinol dose, mg/day, mean (SD)	—	0 (0)	362 (124)	<0.001
Serum urate on allopurinol monotherapy, mmol/l, mean (SD)	—	—	0.50 (0.11)	—
Probenecid dose, g/day, mean (SD)	1.15 (0.59)	1.29 (0.68)	0.99 (0.44)	0.056

* Probenecid monotherapy vs combination therapy. ** Prior to starting any urate-lowering therapy. eGFR: estimated glomerular filtration rate.

Table 2. Changes in serum urate concentrations.

	All Patients				Patients with eGFR < 50 ml/min/1.73 m ²			
	All, n = 57	Probenecid Monotherapy, n = 30	Combination Therapy, n = 27	p*	All, n = 15	Probenecid Monotherapy, n = 9	Combination Therapy, n = 6	p*
Final serum urate, mmol/l, mean (SD)	0.39 (0.09)	0.41 (0.09)	0.38 (0.10)	0.24	0.39 (0.09)	0.42 (0.08)	0.34 (0.05)	0.06
No. (%) achieving target serum urate < 0.36 mmol/l	20 (35)	10 (33)	10 (37)	0.77	5 (33)	2 (22)	3 (50)	0.3
Mean change in serum urate from baseline, mmol/l (SD)	0.21 (0.11)	0.17 (0.11)	0.25 (0.10)	0.004	0.18 (0.11)	0.16 (0.13)	0.22 (0.08)	0.38
Mean percentage change in serum urate from baseline (SD)	33.7 (16.6)	28.6 (17.1)	39.3 (14.4)	0.01	30.9 (16.6)	26.1 (18.0)	38.1 (12.6)	0.18
Mean change in serum urate from allopurinol monotherapy, mmol/l, (SD)	NA	NA	0.12 (0.10)	—	NA	NA	0.11 (0.10)	—
Mean percentage change in serum urate from allopurinol monotherapy (SD)	NA	NA	23.8 (16.4)	—	NA	NA	23.0 (15.8)	—

* Probenecid monotherapy vs combination therapy. eGFR: estimated glomerular filtration rate.

achieved target SU concentrations and those who did not (1.1 g vs 1.2 g daily, respectively; $p = 0.82$). Similarly, eGFR was not significantly different in those who achieved target compared with those who did not (65 vs 59 ml/min/1.73 m²; $p = 0.33$). Logistic regression analysis of all patient data demonstrated that baseline SU concentrations independently predicted achievement of target SU concentrations (Table 3). Other variables included in this analysis, including allopurinol dose, probenecid dose, ethnicity, and eGFR, were not independent predictors of achievement of target SU concentrations.

SU concentrations in probenecid-treated patients with impaired renal function. There were 15 patients with eGFR < 50 ml/min/1.73 m² (median eGFR 41 ml/min/1.73 m², range 22–46): 9 on monotherapy and 6 on combination therapy. Target SU was achieved in 5/15 (33%) of these patients (Table 2). There was no difference in the percentage of patients achieving SU target in those with eGFR < 50 ml/min/1.73 m² compared with those with eGFR ≥ 50 ml/min/1.73 m². For those patients with eGFR < 50 ml/min/1.73 m² treated with monotherapy, mean SU diminished from 0.58 (SD 0.11) mmol/l to 0.42 (SD 0.08) mmol/l ($p = 0.005$). For those patients with eGFR < 50 ml/min/1.73 m² treated with combination therapy, mean SU diminished

from 0.45 (SD 0.08) mmol/l on allopurinol alone to 0.34 (SD 0.05) mmol/l after addition of probenecid ($p = 0.04$). There were only 4 patients with eGFR < 30 ml/min/1.73 m². The mean SU in these patients diminished from 0.53 to 0.43 mmol/l, but none of these patients achieved SU target. In contrast, 5/11 of the patients (45%) with eGFR between 30 and 50 ml/min/1.73 m² achieved SU target.

Tolerability of probenecid. Adverse events attributed to probenecid were observed in 10/57 patients (18%). One (1.8%) patient developed painful tongue, 2 (3.5%) developed headache, 1 (1.8%) had mouth ulcers, 2 (3.5%) had rashes, and 3 (5.3%) patients developed gastrointestinal side effects. One (1.8%) patient developed urolithiasis; this patient had a history of kidney stones and the calculus was not analyzed for its composition. Probenecid was discontinued in 7/57 patients (12%) because of adverse events. Adverse events attributed to probenecid were observed in 8/42 patients (19%) with eGFR ≥ 50 ml/min/1.73 m² and in 2/15 patients (13%) with eGFR < 50 ml/min/1.73 m².

DISCUSSION

Our study demonstrated that in clinical practice probenecid is a moderately effective agent to reduce SU concentrations in patients with gout. At the relatively low doses used in this study (1.15 g per day), most patients tolerate probenecid well and can continue this medication without adverse events. In particular, the rates of urolithiasis were low. Patients in our study represent those requiring complex management because of intolerance/contraindications to allopurinol or failure of allopurinol monotherapy to achieve SU targets. In more than a third of these patients, prescription of probenecid allowed target SU < 0.36 mmol/l to be achieved.

Our findings can be compared with other studies of probenecid that have been reported in the “treat to SU target” era. Overall, the reductions in SU observed in our

Table 3. Logistic regression analysis of predictors of target serum urate < 0.36 mmol/l (n = 57).

Variables	B	SE	p
Allopurinol dose	0.003	0.002	0.198
Probenecid dose	0.573	0.575	0.319
Baseline serum urate	-8.950	4.243	0.035
Non-Polynesian ethnicity	1.279	0.656	0.051
Estimated glomerular filtration rate	0.017	0.016	0.283
Constant	0.609	2.608	0.815

R² = 0.25, chi-square = 11.348, p for model < 0.05.

patients were smaller than those previously reported. We observed a 29% reduction in SU concentrations with probenecid monotherapy. In contrast, Reinders and colleagues reported a 50% reduction in SU concentrations in 35 patients treated with fixed-dose (2 g/day) probenecid monotherapy because of failure of allopurinol monotherapy²¹. In addition to differences in doses and prescribing of probenecid in that study, patients with creatinine clearance < 50 ml/min were specifically excluded, and the median creatinine clearance was > 80 ml/min. We observed a 39% reduction in SU concentrations from baseline, and 23% reduction in SU from allopurinol monotherapy levels, with allopurinol and probenecid combination therapy. In a report of 14 patients on allopurinol treatment, Reinders and colleagues reported a decrease in SU of 53% from baseline with allopurinol and probenecid (1 g/day) combination therapy²². Again, in their study, patients with significant renal impairment were excluded. Stocker and colleagues described 20 patients with gout who were treated with allopurinol and probenecid combination treatment²³. In that study, SU decreased by 21% in those treated with probenecid 500 mg daily and 37% in those treated with probenecid 1 g daily from allopurinol monotherapy levels. Although patients were taking similar allopurinol doses, there were lower rates of renal impairment. It is uncertain whether increasing the probenecid dose would have led to higher numbers of patients achieving target SU concentrations. Prospective studies examining the role of probenecid dose escalation to target SU concentrations will be of great interest. Future head-to-head studies between probenecid and new ULT agents such as febuxostat will also be of importance in determining the appropriate second-line strategy for those patients with incomplete response or intolerance to allopurinol.

Thus, the lower percentage reductions in SU in our study compared with previous studies may reflect the degree of chronic kidney disease in our patients. However, our study demonstrated that patients with eGFR between 30 and 50 ml/min/1.73 m² can respond to probenecid. One-third of patients with eGFR < 50 ml/min/1.73 m² achieved target SU with probenecid therapy. The number of our patients with eGFR < 30 ml/min/1.73 m² was small, but even these patients had some reduction in SU concentrations, although not sufficiently low to achieve SU target. Further, the logistic regression analysis did not identify eGFR as an independent predictor of failure of probenecid to achieve SU targets. In addition, most of our patients with chronic kidney disease tolerated probenecid. These data, together with other reports that probenecid has modest urate-lowering effects in patients with renal impairment^{4,23}, argue that judicious use of probenecid can be considered in patients with mild-moderate renal impairment, particularly if other urate-lowering agents are not available or are contraindicated. SU concentrations should be carefully

monitored in this context, and probenecid should be discontinued if SU reductions are not observed or if adverse events develop.

We acknowledge the limitations inherent in a retrospective observational study. The percentage of patients with eGFR < 50 ml/min/1.73 m² was small, and may reflect clinicians' caution about prescribing probenecid in patients with moderate renal impairment. Doses of probenecid were not prespecified or standardized, but were selected according to the treating physicians' clinical judgment. This study did include high numbers of Maori and Pacific people, consistent with the high prevalence of severe gout in these populations. Importantly, regression analysis did not identify ethnicity as a significant independent predictor of achieving a target SU concentration with probenecid therapy. Adherence to probenecid was not assessed, and it is likely that some failures to achieve SU target were due to nonadherence rather than true medication failure. Previous studies reported adherence rates of 20%–70% with urate-lowering agents in clinical practice^{24,25}. Patients were all identified from secondary care rheumatology clinics and it is possible that achievement of SU targets may have been different in patients with less complex disease treated in primary care. Nevertheless, we believe that the data do contribute to further understanding about this widely available and cost-effective agent.

Our study demonstrated that probenecid is a moderately effective urate-lowering agent in daily clinical management of patients with complicated gout who have a lack of efficacy or intolerance to allopurinol. In this group, probenecid prescription allows target SU concentrations to be achieved in at least a third of patients. Patients with eGFR < 50 ml/min/1.73 m² generally tolerate probenecid and may have a clinical response. Our data support the recommendations regarding probenecid in the 2012 ACR guidelines¹² for gout management, and highlight probenecid as a useful agent to consider in patients with complex gout.

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