Furosemide increases plasma oxypurinol without lowering serum urate—a complex drug interaction: implications for clinical practice

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Abstract

Objective. To determine the effects of furosemide on serum urate (SU), plasma oxypurinol and urinary urate.

Methods. Twenty-three cases with gout receiving furosemide and allopurinol were recruited. Twenty-three controls with gout receiving allopurinol but no diuretics were matched on age, gender, estimated glomerular filtration rate and allopurinol dose. SU, plasma oxypurinol and urinary urate were assessed on a single occasion. The effects of a single dose of furosemide 40 mg were examined in a separate group of 10 patients receiving allopurinol but not diuretic.

Results. Cases had significantly higher SU and plasma oxypurinol compared with controls despite receiving similar doses of allopurinol. There was no difference in urinary urate excretion. There was a significant increase in area under the curve (AUC)₀⁻₂₄ for oxypurinol after administration of furosemide 40 mg.

Conclusion. The interaction between allopurinol and furosemide results in increased SU and plasma oxypurinol. The exact mechanisms remain unclear but complex interactions that result in attenuation of the hypouricaemic effects of oxypurinol are likely.


Key words: gout, allopurinol, oxypurinol, furosemide, serum urate.

Introduction

The metabolic syndrome consists of multiple interrelated conditions including hypertension, hyperlipidaemia, insulin resistance/diabetes and obesity, and is associated with an increased risk of cardiovascular disease [1]. The prevalence of the metabolic syndrome among patients with gout is 62.8% compared with 25.4% in patients without gout [2]. As such, many patients with gout are receiving additional medications that may have effects on uric acid production and/or excretion. Recent evidence from the UK and Germany suggests that ~18% of patients with gout have concomitant hypertension and ~7–10% have concomitant heart failure [3]. Both these conditions are commonly treated with diuretics, in particular loop or thiazide diuretics, which increase serum urate (SU) concentrations. Furosemide is a powerful loop diuretic that decreases urinary uric acid excretion, which along with the reduction in extracellular fluid, results in hyperuricaemia. The increase in SU occurs within a few days of commencing diuretics and persists for the duration of therapy [4].

In a retrospective study of 9249 patients with no history of therapy for gout, the relative risk for initiation of anti-gout therapy within 2 years of commencement of anti-hypertensive therapy was examined. In patients receiving non-thiazide anti-hypertensives the relative risk was 1.0 (95%CI 0.65, 1.53) compared with 1.99 (95%CI 1.21, 3.26) for patients on thiazide diuretics and 2.29 (95%CI 1.55, 3.37) for patients on both. Furthermore, the risk increased significantly when thiazide doses exceeded 25 mg daily [5]. In a more recent study,
the odds ratio for use of a thiazide diuretic in the 24 h before an acute attack of gout was 7.3 [6].

Allopurinol is rapidly metabolized to oxypurinol, which by virtue of its longer half-life exerts most of the urate lowering effect via inhibition of xanthine oxidase. Furosemide has been shown to reduce urinary excretion of oxypurinol. In a small study of six healthy subjects, a single i.v. dose of 20mg furosemide reduced urinary oxypurinol excretion by ~40%, although there was no effect on serum oxypurinol concentrations during the study period [7]. However, a significant interaction between furosemide and allopurinol may occur during long-term treatment, and the authors suggest that the hypouricaemic effect of allopurinol may become more potent as a result of this interaction [7]. This does not reflect clinical practice where those patients receiving diuretics are often more difficult to treat successfully with urate lowering therapy such as allopurinol. We have shown previously that concomitant use of furosemide resulted in a significantly higher plasma oxypurinol concentration for any given allopurinol dose compared with patients who were not prescribed furosemide [8]. However, patients on furosemide required relatively higher doses of allopurinol to achieve the target SU of <0.36mmol/l required for successful long-term control of gout [9]. On the basis of these observations, we hypothesized that allopurinol becomes a less-effective urate lowering therapy in patients receiving concomitant furosemide.

The aims of this study were to determine the extent to which long-term treatment with allopurinol and furosemide results in increased SU and the effects on plasma oxypurinol concentrations. In addition, we wished to examine the effects of a single oral dose of furosemide on the pharmacokinetics of allopurinol and oxypurinol as well as the effects on SU and urinary urate excretion.

Patients and methods

There were two parts to this study: (i) a case–control study and (ii) a pharmacokinetic study. Both were undertaken in Christchurch, New Zealand. Ethical approval was obtained from the Upper South A Regional Ethics Committee, New Zealand. Written informed consent was obtained from each patient. The study was registered with the Australian New Zealand Clinical Trials Registry (12609000529246).

Case–control study

Twenty-three patients with gout as defined by ARA criteria [10] on a stable dose of allopurinol and furosemide for ≥1 month were enrolled (cases). One month of furosemide therapy before enrolment was considered sufficient to achieve steady state and for any effect on SU to have occurred. For each case, a single control with gout on stable dose allopurinol, but not receiving furosemide or any other diuretic, was enrolled. Cases and controls were matched on age ± 10 years, gender, allopurinol dose ± 50mg/day and estimated glomerular filtration rate (eGFR) as determined by the Modification of Diet in Renal Disease (MDRD) study equation [11]. The eGFR bands used for matching were as follows: <5, 5–15, 15–30, 30–50, 50–70, 70–90, 90–110, 110–130 and >130 ml/min.

Clinical and laboratory assessment

Patients were seen on a single occasion and standardized data were collected for all cases and controls. Patient demographic and clinical details were collected, including associated medical conditions and medications. Laboratory assessment included full blood count, renal and liver function, SU, plasma oxypurinol and allopurinol, and random urinary urate and creatinine. Blood samples were collected 6–9h following the allopurinol dose. Allopurinol and oxypurinol were measured as previously described [9]. The Simkin index was calculated as previously described [12].

Pharmacokinetic study

Ten patients with gout who had been on a stable dose of allopurinol for at least 1 month and who were not receiving furosemide or any other diuretic were recruited. Participants were fasted from midnight before study visits and were required to be alcohol free on the day before, and day of, each visit. Serial blood samples were taken at baseline, 30 min, 1, 2, 4 and 24 h. Full blood count, liver function, creatinine, potassium, urate, allopurinol and oxypurinol concentrations were assessed at baseline. Samples at subsequent time points were analysed for creatinine, urate, allopurinol and oxypurinol concentrations. Twenty-four-hour urine collection for urinary urate excretion was also undertaken.

The regular doses of allopurinol and any other prescribed medications were given immediately after the baseline blood sample had been acquired. Half of the participants received no furosemide on day one and returned the next day to receive furosemide. The other half of the participants received furosemide on day one and returned 2 days later to receive no furosemide, to allow sufficient time for the furosemide to be washed out.

During the visits, participants were provided with the same low purine meals for breakfast, morning tea and lunch. Each participant completed a diet sheet outlining what they had eaten the day before their visit and any extra food consumed during the study period.

Statistical analysis

Case–control analysis

Clinical and demographic features were compared between cases and controls using independent t-tests and χ²-tests. The relationships between SU, plasma oxypurinol and Simkin index were explored using conditional logistic regressions, which allowed for the matching of cases and controls.

Pharmacokinetic study

The pharmacokinetic parameters [area under the curve (AUC)₀−₂₄, tₘₐₓ, cₘₐₓ] were estimated using non-compartmental models. The AUC₀−₂₄ was estimated using the log-linear trapezoidal rule and tₘₐₓ was

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calculated as the time to the maximum measured concentration as $c_{\text{max}}$. Comparisons of these parameters between furosemide and no furosemide were undertaken using the non-parametric Wilcoxon signed-rank test. Two-tailed $P$-value $<0.05$ was taken to indicate statistical significance.

Results

Case-controlled study

Patients and demographics

The demographics and clinical features of the 23 cases and controls are outlined in Table 1. Adequate matching between cases and controls was achieved (Table 1). More cases had hypertension and/or ischaemic heart disease, however, reflecting their use of furosemide. The mean dose of furosemide in the cases was 138.7 mg/day (range 20–1000 mg/day, median 80 mg/day). The median duration of furosemide therapy was 24 months (1–96 months). Cases and controls were not matched for other drugs that might affect SU. Sixteen cases and 12 controls were receiving aspirin, and two cases and two controls were receiving atorvastatin, both drugs that can increase SU. Four cases were receiving losartan that can lower SU.

Effects of furosemide on SU and plasma oxypurinol concentrations

Cases had significantly higher SU concentrations 6–9 h after allopurinol dose compared with controls (mean (S.E.M.) SU; cases 0.41 (0.014) mmol/l (0.30–0.58 mmol/l) vs controls 0.35 (0.014) mmol/l (0.23–0.53 mmol/l; $P = 0.006$) despite receiving similar doses of allopurinol. This equates to a large effect size of 1. There was no effect of aspirin ($P = 0.49$) or losartan ($P = 0.52$) on SU, nor was there any effect of these two drugs on the difference in SU between cases and controls. Cases also had significantly higher concentrations of plasma oxypurinol compared with controls, despite receiving similar doses of allopurinol ($P = 0.029$) (Fig. 1). There was no effect of aspirin ($P = 0.44$) or losartan ($P = 0.52$) on plasma oxypurinol concentrations. There was also no effect of aspirin on the difference in plasma oxypurinol between cases and controls. However, the difference in plasma oxypurinol between cases and controls was no longer significant when losartan was included in the model ($P = 0.053$).

Effect of furosemide on urinary urate excretion

The Simkin index was calculated as an estimate of urinary urate excretion. There was no significant difference in the Simkin index between cases and controls [mean (S.E.M.) cases 0.177 (0.021) mg/dl vs controls 0.181 (0.21) mg/dl; $P = 0.9$].

Multiple logistic regression that allowed for the matching of cases and controls (matching included age, eGFR, and allopurinol dose) and also included the Simkin index as a covariate showed that cases had significantly higher SU and plasma oxypurinol concentrations compared with controls ($P < 0.05$ for both).

Pharmacokinetics study

Effects of furosemide on the pharmacokinetics of allopurinol and oxypurinol

The effects of a single dose of furosemide 40 mg orally on the pharmacokinetics of allopurinol, oxypurinol and SU were examined. The demographics of the 10 patients are outlined in Table 2.

There was a significant increase in AUC$_{0\rightarrow24}$ for oxypurinol and SU after administration of furosemide 40 mg. However, there was no significant change in AUC$_{0\rightarrow24}$ for allopurinol (Table 3 and Fig. 2). There was no significant difference in any of the other pharmacokinetic variables (Table 3).

Although urinary urate concentration decreased during the 24-h period after the administration of furosemide, there was no significant difference in total urinary urate excretion (Table 3).

Table 1

Demographics details of 23 cases (co-prescribed furosemide) and matched controls

<table>
<thead>
<tr>
<th></th>
<th>Cases ($n = 23$)</th>
<th>Controls ($n = 23$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, years</td>
<td>69.04 (9.4)</td>
<td>68.8 (10.1)</td>
<td>0.94</td>
</tr>
<tr>
<td>Male, %</td>
<td>91.3</td>
<td>91.3</td>
<td></td>
</tr>
<tr>
<td>Creatinine, mmol/l</td>
<td>131.2 (27.9)</td>
<td>125.2 (37.1)</td>
<td>0.28</td>
</tr>
<tr>
<td>eGFR, ml/min</td>
<td>50.9 (13.5)</td>
<td>54.3 (15.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Allopurinol dose, mg/day</td>
<td>191.3 (88.7)</td>
<td>197.8 (87.2)</td>
<td>0.80</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>16</td>
<td>18</td>
<td>0.67</td>
</tr>
<tr>
<td>Maori or Pacific Island</td>
<td>7</td>
<td>2</td>
<td>0.06</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>3</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>30.7 (4.5)</td>
<td>30.8 (4.6)</td>
<td>0.91</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8</td>
<td>6</td>
<td>0.52</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20</td>
<td>11</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypercholesterolaeima</td>
<td>10</td>
<td>13</td>
<td>0.38</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>22</td>
<td>12</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

Data are presented as mean (s.d.).
Discussion

Improvement in clinical outcomes for patients with gout requires sustained reduction in SU to <0.36 mmol/l (<6 mg/dl), or lower if there are tophi present [13]. The combination of furosemide and allopurinol is common in clinical practice. Herein we have shown that concomitant therapy with allopurinol and furosemide results in higher SU concentrations despite higher plasma oxypurinol concentrations. These data confirm our hypothesis that allopurinol is a less effective urate lowering therapy in patients receiving concomitant furosemide. While we have not specifically studied thiazide diuretics, a similar effect is likely to be observed.

The exact mechanisms of the observed interactions remain unclear. SU and oxypurinol concentrations result from a balance between production and renal excretion. A variety of uric acid transporters have been identified within the kidney. Apical organic anion transporter (OAT4) and urate transporter (URAT1) resorb filtered urate from the urine into tubular cells within the proximal tubule. Multi-drug resistance protein (MRP) 4 has been identified as another urate efflux transporter within the kidney. Furosemide has been reported to decrease the fractional clearance of oxypurinol [7]. Furosemide and hydrochlorothiazide have been shown to inhibit MRP4-mediated urate transport in human embryonic kidney cells. Furthermore, allopurinol and oxypurinol stimulated MRP4-mediated urate transport [14]. URAT1 is also implicated in renal reabsorption of oxypurinol, an effect that may be inhibited by uric acid [15]. Whether furosemide has any effect on URAT1 remains unknown. Thus there are complex interactions between urate and oxypurinol transport mechanisms within the kidney that may be altered by co-administration of diuretics such as furosemide. Polymorphisms within several of these genes have been identified, and these may influence the response to therapy.

**Table 3** Pharmacokinetic parameters of plasma oxypurinol, allopurinol, urate and urinary urate in 10 patients with and without furosemide

<table>
<thead>
<tr>
<th></th>
<th>No furosemide</th>
<th>Furosemide</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allopurinol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AUC_{0-24}), (\mu\text{mol/l}\cdot\text{h})</td>
<td>31.8 (10.2−95.6)</td>
<td>41.8 (8.8−75.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>(c_{\text{max}}, \mu\text{mol/l})</td>
<td>11.5 (4.4−37.9)</td>
<td>15.4 (4.2−29.2)</td>
<td>0.72</td>
</tr>
<tr>
<td>(t_{\text{max}}, \mu\text{mol/l})</td>
<td>1.0 (0.5−4)</td>
<td>0.75 (0.5−1.0)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Oxypurinol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AUC_{0-24}), (\mu\text{mol/l}\cdot\text{h})</td>
<td>1852.5 (1013.3−2814.1)</td>
<td>2101.3 (905.3−2973.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>(c_{\text{max}}, \mu\text{mol/l})</td>
<td>90.6 (51.2−129.2)</td>
<td>103.0 (43.7−137.9)</td>
<td>0.17</td>
</tr>
<tr>
<td>(t_{\text{max}}, \mu\text{mol/l})</td>
<td>4.0 (1.0−4.0)</td>
<td>4.0 (0.5−4.01)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Urate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AUC_{0-24}), (\mu\text{mol/l}\cdot\text{h})</td>
<td>6.8 (5.0−9.5)</td>
<td>7.7 (5.6−10.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>24-h urine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume, ml</td>
<td>2239 (1389−3802)</td>
<td>3157 (1276−4380)</td>
<td>0.059</td>
</tr>
<tr>
<td>Urate, mmol/l</td>
<td>1.1 (0.5−2.4)</td>
<td>0.75 (0.3−1.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Creatinine, mmol/l</td>
<td>7.2 (2.1−13.3)</td>
<td>5.4 (2.5−12.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Urate excretion, mmol/24 h</td>
<td>2.2 (0.7−5.8)</td>
<td>1.9 (0.5−3.1)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Data are presented as median (range).
associated with gout and hyperuricaemia [16]. Whether gene-diuretic interactions further influence SU and gout is unknown.

Our data suggest that the net effect of co-prescribed furosemide is retention of both oxypurinol and urate. This effect is observed even after a single dose of oral furosemide, resulting in a higher AUC$_{0-24}$ for oxypurinol and SU, suggesting reduced clearance of both.

Despite higher plasma oxypurinol concentrations, patients receiving furosemide have higher SU concentrations. There is currently no established therapeutic range for plasma oxypurinol to achieve the target SU <0.36 mmol/l (6 mg/dl) [8]. It seems plausible that the oxypurinol target range will need to be higher in patients on furosemide and other diuretics.

Interestingly, there was no difference in urinary urate excretion as assessed by the Simkin index in patients on long-term furosemide and in patients after a single dose of oral furosemide, as assessed by 24-h urine. There are a number of potential explanations for these observations. Both 24-h urine collection and the Simkin index have technical issues that may impact on their reliability [12]. Biological factors, in particular dietary purine intake, are responsible for most of the variation in urinary urate excretion. Although we controlled the diet in the pharmacokinetic study, there was variation in dietary

![Fig. 2 AUC$_{0-24}$ for (A) allopurinol, (B) oxypurinol and (C) urate.](https://academic.oup.com/rheumatology/article-abstract/51/9/1670/1791626)
intake in the case-controlled study that could not be precisely quantified and adjusted for. As noted above, oxypurinol and furosemide have opposing effects on the MRP4 urate efflux transporter within the kidney, and the balance between these effects may therefore alter urine urate excretion. A decrease in urate production as a result of allopurinol, may result in less urate available for excretion and therefore potentially a higher fractional tubular resorption. Furosemide has also been reported to result in decreased urinary excretion of oxypurinol and xanthine by 39 and 43%, respectively, with no change in urinary hypoxanthine excretion in patients receiving allopurinol [7]. In healthy subjects, not receiving allopurinol, furosemide has been reported to reduce urinary excretion of hypoxanthine by 47%, xanthine by 49% and uric acid by 49% [17]. These data suggest that furosemide may decrease purine degradation or may have an inhibitory effect on xanthine oxidase.

It has been suggested that there is an increased risk of allopurinol hypersensitivity in those patients receiving allopurinol and furosemide [18]. While the current study was not designed to determine adverse effects with the allopurinol furosemide combination, our previous data have not suggested an increased risk with this combination despite higher oxypurinol concentrations [9].

Although the underlying mechanisms are complex, our study reinforces the importance of clinicians carefully considering the indications for use of loop or thiazide diuretics in patients with gout and other co-morbidities including those related to the metabolic syndrome. Alternative agents, which do not result in retention of uric acid, should be used. For example, the angiotensin II receptor antagonist losartan has uricosuric effects and reduces SU by 10–20% [19]. Losartan has been reported to be useful in helping to prevent thiazide-induced increases in SU [20]. The calcium channel blocker amlodipine, another effective anti-hypertensive agent, also increases uric acid clearance and reduces SU concentrations [21]. Statins are the most commonly prescribed lipid lowering drugs and in patients with primary hyperlipidaemia atorvastatin, but not simvastatin, results in a reduction of SU [22]. Fenofibrate, but not other fibrates, has been shown to reduce SU through enhanced uric acid clearance [23] and in patients receiving allopurinol or benzbromarone the addition of fenofibrate results in further reduction in SU [24].

To date there is no therapeutic range for plasma oxypurinol concentrations. Our data suggest that such a range may need to be modified for patients on furosemide (and presumably other diuretics). Further studies will be required to validate this.

In summary, there is a significant interaction between allopurinol and furosemide that results in increased SU and plasma oxypurinol concentrations. The exact mechanisms remain unclear but are likely due to complex interactions that result in furosemide attenuating the hypouricaemic effects of allopurinol and oxypurinol. Clinicians need to regularly review and question the need for furosemide in gout patients treated with allopurinol.

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References


