Allopurinol dosing in renal impairment

Dear Editor

In the recent article entitled "Managing patients with renal colic in primary care: Know when to hold them", BPJ 60 (Apr, 2014), it states: "Allopurinol is indicated for the prophylaxis and treatment of patients with either urate or calcium oxalate stones...Lower doses of allopurinol are recommended for patients with estimated glomerular filtration rates less than 60 mL/min/1.73m^2."

Dr Linda Bryant, in a December 2011 article in the Journal of Primary Health Care states: "Treat the target serum uric acid concentration rather than according to renal function. This has been shown to be safe and effective"

Your comments please.

Dr Murray Hing
General Practitioner
Auckland

In 1984 a seminal paper on allopurinol toxicity in patients with renal insufficiency was published.[1] For many years this study served as the basis for allopurinol dosing guidelines due to its conclusion that there is a direct relationship between severe allopurinol toxicity and decreased creatinine clearance. Dr Bryant quite rightly points out in the article "Allopurinol – dose according to effect, not renal function" that current guidelines no longer support allopurinol dose adjustments based on the study from 1984.[2] Our renal colic article did not cover allopurinol dosing in any detail, however, this change in practice was highlighted in our article "An update on the management of gout" BPJ 51 (Mar, 2013) by the statement:

"*…recent evidence has shown no increase in serious toxicity with higher doses of allopurinol.*" Nonetheless, renal function should still be carefully considered for safety reasons when initiating allopurinol in patients with gout. A "start low and go slow" method of titrating the patient's allopurinol dose is recommended to avoid adverse reactions; mainly skin, subcutaneous and immune system reactions, as well as reducing the likelihood of precipitating gout attacks.

The majority (70%) of the active metabolite of allopurinol, oxypurinol, is excreted by the kidneys.[3] In patients with renal impairment, oxypurinol accumulates due to inadequate renal clearance.[4] In some patients, accumulated levels of oxypurinol may contribute to delayed hypersensitivity reactions, referred to as the allopurinol hypersensitivity syndrome (AHS). This is a rare but serious adverse effect of allopurinol treatment, characterised by rash, eosinophilia, leukocytosis, fever, hepatitis and renal failure.[5] AHS is reported to occur in 0.1% to 0.4% of patients taking allopurinol and is reported to have a mortality rate of over 25%.[4] In March 2014, Medsafe added allopurinol to the medicines monitoring scheme due to concerns about lichenoid-type (medicine-induced) skin reactions.[6]

Risk factors for AHS include:[4, 5]

- Initiation of allopurinol treatment within the last four to six weeks
- Renal impairment
- A high starting dose of allopurinol relative to renal function
- The HLA-B5801 genotype that is most prevalent in people of Asian descent

The clinical significance of reduced renal function in patients taking allopurinol is emphasised by international estimates that between 40% to 50% of patients with gout also have chronic kidney disease (CKD).[4]

Dr Bryant largely bases the recommendation to focus less on renal function when dosing allopurinol on a study published by Stamp *et al*, 2011, which concluded that "*increasing the dose of allopurinol above the proposed creatinine clearance-based dose led to a significant reduction in the serum urate concentration.*"[7] However, there is one important point to note about the patients in this study: the patients with gout who were recruited had already been receiving a stable dose of allopurinol for at least one month. Therefore, one important risk factor for AHS, i.e. the recent initiation of allopurinol, was excluded from the patient cohort. In 2012, Stamp *et al* published another study showing that a high starting dose of allopurinol relative to renal function was also a risk factor for AHS.[5] This paper suggested starting doses for patients with reduced renal function, and these were published in our 2013, BPJ article "An update on the management of gout".[5]

Stamp *et al*, 2012, concluded: "*In summary, we have shown that the starting dose of allopurinol is an important risk factor for the development of AHS… Progressive up-titration of allopurinol is not associated with an increased risk of AHS, and once allopurinol treatment is established, this strategy should be adopted to achieve the target serum urate level.*"[5]

Renal function is therefore an important factor in determining the starting dose of allopurinol, from which point doses can then be slowly and relatively safely titrated upwards, until the patient achieves the target serum uric acid concentration of less than 0.36 mmol/L. Dr Bryant suggests starting all patients with gout on allopurinol 150 mg, daily, and doubling the dose to 300 mg, daily, after four weeks.[2] However, according to Stamp *et al*, 2012, this starting dose is only appropriate for patients with a estimated glomerular filtration rate (eGFR) of 91 – 130 mL/min/1.73m^2.[5] For example, the appropriate starting dose for a patient with an eGFR of between 46 – 60 mL/min/1.73m^2 is allopurinol 50 mg, alternating with allopurinol 100 mg, every other day.[5]

The challenge for the clinician when prescribing allopurinol to a patient with reduced renal function is to lower the serum urate level in order to prevent either attacks of gout or kidney stone formation, without the occurrence of the hypersensitivity reactions that are more likely to occur within the first six weeks of starting the medicine. A one-size fits all approach to dosing of allopurinol treatment is unlikely to achieve this goal and may put some patients at risk; treatment should be individualised.

In regards to the management of urinary stones – lifestyle measures are first-line in the prevention of urinary stone formation, e.g. increasing water intake, reducing salt intake and avoiding foods rich in oxalate and fructose-containing soft

drinks. The majority of urinary stones contain calcium oxalate, and potassium citrate is subsidised under Special Authority for patients with recurrent calcium oxalate urinary stones. Allopurinol should be reserved for patients with either calcium oxalate or urate stones, and elevated serum urate levels.[8] There is currently no consensus on what the target serum urate level should be when treating patients with a history of urinary stones. Any reduction in serum urate is likely to be beneficial, but a reasonable approach would be to treat to a target serum urate level less than 0.36 mmol/L. Serum urate, creatinine and LFTs should be monitored during allopurinol dose titration.

ACKNOWLEDGEMENT: Thank you to **Professor Lisa Stamp**, Rheumatologist, Department of Medicine, University of Otago, Christchurch for expert review of this response.

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Non-pharmacological management of pain

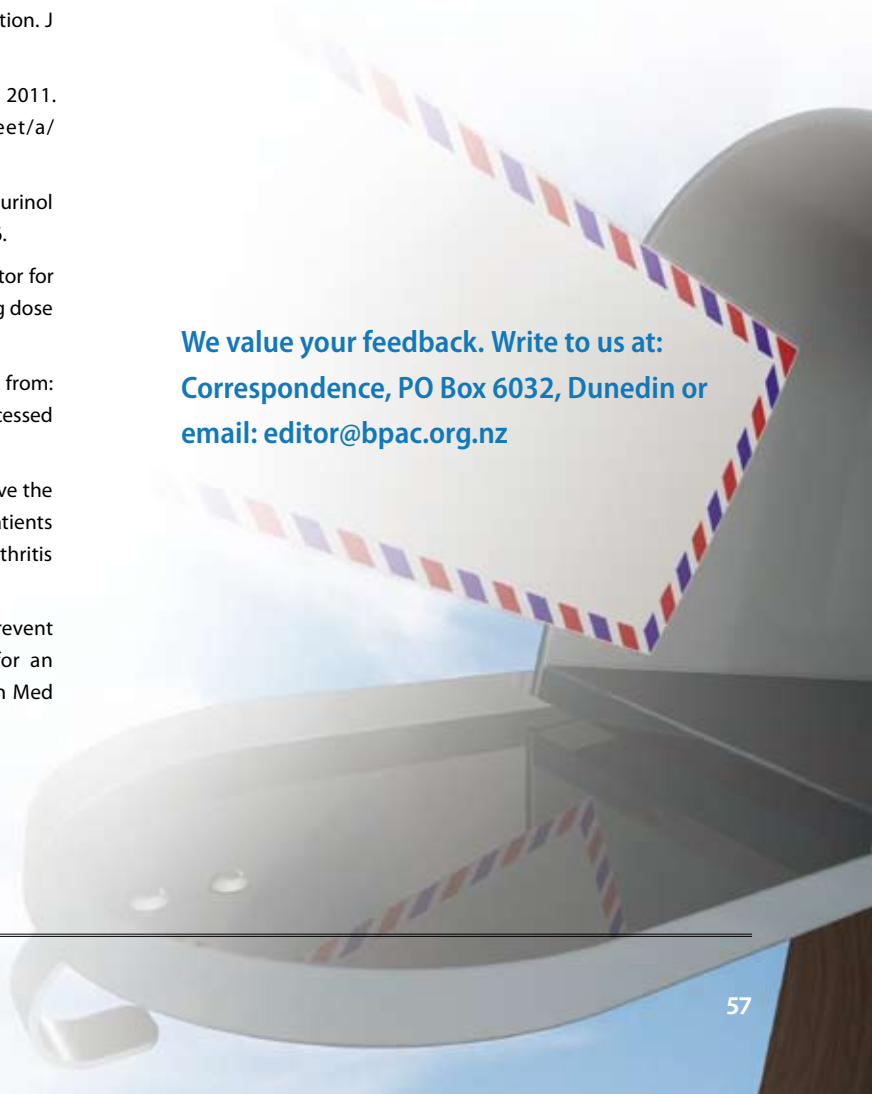
Dear Editor

Reading the March issue of Best Practice Journal, regarding managing pain in children, I was prompted to write about another useful tool - smartphone games. I was recently able to remove some very large splinters from a young boy's foot while he was absorbed in a game. Before we thought of this he would not keep still enough, but while playing he barely felt it.

I have also had an anxious adult patient use similar games to keep her mind off minor surgery, and it would probably also work for immunisations!

Dr Joanna Joseph
General Practitioner
Wellington

Thank you for your contribution. We would love to hear about "Best Practice Tips", on any subject, from our readers.



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