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Letter

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Allopurinol in renal insufficiency: a reappraisal

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Abstract

Worldwide, gout is the most common inflammatory arthropathy, and its treatment is often complicated by the co-presence of renal insufficiency. Renally impaired gout patients are generally undertreated with urate-lowering agents due to fears of serious side effects, but a recent study suggests that more aggressive treatment may be safer than previously thought.

Key words: Gout, renal insufficiency, allopurinol.

Dear Editor,

Patients with gout have a high incidence of concomitant renal disease, complicating the use of anti-hyperuricemic agents.[1] The greatest concern is for provoking allopurinol hypersensitivity syndrome (AHS), a potentially life-threatening condition. In a seminal paper, Hande et al. collated 78 AHS case reports and concluded that the most common predisposing factor was renal insufficiency.[2] Hande et al. also prospectively investigated the metabolism of allopurinol and its main active metabolite, oxyopurinol, in both healthy subjects and those with renal insufficiency. Their conclusion, based on their review of the available data from patients who had experienced hypersensitivity reactions, as well as their prospective data on allopurinol/oxypurinol metabolism as it related to renal function, was that increased oxypurinol levels in those with renal insufficiency directly correlated to the risk of incurring allupurinol hypersensitivity. Based on these observations, Hande et al. made recommendations regarding appropriate allopurinol dosing based on creatinine clearance, and over the years, these recommendations have been adhered to rigidly.

While the Hande's recommendations were not unreasonable, one unintended consequence has been a tendency by physicians to undertreat gout patients with chronic renal insufficiency. Given the importance of appropriately treating gout, Hande's methodology, results and conclusions at least deserve ongoing scrutiny. Indeed, a look back at that study identifies several limitations endemic to their methodologic approach. One problem is that the paper gives no epidemiologic data regarding the incidence of AHS; i.e., no denominator. Were the 78 patients presented in the study, all of whom had AHS, culled from a population of 300, 3.000, or 3.000,000? Was this incidence greater than that of patients without renal insufficiency (probably, but not defined in the study.) Although AHS incidence has been estimated at 0.4%, a compendium of case reports cannot provide utilizable information as to the absolute risk of developing the condition. Additionally, although the study showed that oxypurinol levels were higher in patients with renal impairment, causality was never established between higher oxypurinol concentration and allopurinol hypersensitivity. Regardless of generalizability, Hande et al.'s recommendations

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have contributed to a pattern of chronic allopurinol underdosing in renally-impaired patients, to the point where the majority of such patients fail to achieve the recommended target urate of <6 mg/dL. Despite this undesirable outcome, almost no additional research has been performed to validate Hande's treatment algorithm.

Into this murky background Stamp et al. beam some much needed light.[3] Stamp et al. enrolled 90 gout patients with renal insufficiency (mean CrCl=66.8 mL/minute) already taking allopurinol, and titrated the allopurinol to target (<6 mg/dL), regardless of Hande's recommendations. The 83 patients who completed the study included several whose baseline serum urate levels were already at target, as well as others whose urate levels were >6 mg/dL but were allopurinol-underdosed even according to the Hande criteria, and whose urate levels normalized when the correct Hande dosing was implemented. However, 45 remained hyperuricemic despite adherence to the Hande guidelines, and these subjects had allopurinol titrated until reaching the target serum urate level. Of the 45 patients who underwent dose titration beyond the Hande criteria, 35 completed the study. Three of 10 who dropped out did so due to the development of a rash, although none developed AHS. Of the 35 subjects who completed the study, 31 achieved the target serum urate at or before the 12-month visit. The mean increase in allopurinol dosage above that of the Hande recommendations for this group was 114 mg (final dose of 335.7 mg).

Taken together, these data suggest that judiciously increasing allopurinol to doses above those recommended by Hande could provide appropriate efficacy in almost all patients, without serious adverse events. Reassuringly, despite having a mean CrCl of 62 mL/minute, none of the 45 patients in the dose-escalation group developed AHS.

A few caveats must be noted before applying this approach to the clinic. One is the small sample size of Stamp et al.'s study; since AHS is relatively rare, the study may have been inadequately powered. Additionally, 4/45 patients (9%!) in the dose-escalation arm had an allopurinol-associated rash. Were these rashes a prodrome that might have progressed to AHS in a less-closely monitored setting? Importantly, the dose-escalation group had, on average, only modestly elevated serum urates at the outset (mean=7.1 mg/dL), so only limited dose escalation was required for most subjects. Moreover, even if these findings are reproduced on a larger scale, the study's specific protocol may be too laborious to be practicably adopted in the clinic. Implementing Stamp's protocol requires not only access to Hande's 1984 recommendations, but also an ability to implement both monthly titration and close clinical/laboratory monitoring. That may be a tall order in primary care, especially since other urate-lowering medications may be safe and effective for patients with gout and concomitant renal insufficiency, without the need for complex dosing and titration schedules.

What can be concluded from this small but provocative study? Certainly, a larger study is needed. But ultimately, Stamp's study may be the first crack in the long- and wide-held belief that patients with gout and renal insufficiency cannot be both aggressively (but carefully!) and appropriately treated with allopurinol.

References

1. Keenan R, O'Brien WR, Lee KH, et al. Prevalence of contraindications and prescription of pharmacologic therapies for gout. *Am J Med* 2011;124;155-63.
2. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med* 1984;76:47-56.
3. Stamp LK, O'Donnell JL, Zhang M, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. *Arthritis Rheum* 2011;63:412-21.

