ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should patients with gout avoid thiazides for hypertension?

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Drugs mentioned in this article

allopurinol (Zyloprim)
aspirin
chlorthalidone (Thalitone)
febuxostat (Uloric)
hydrochlorothiazide
losartan (Cozaar)

A: The decision should be individualized, taking into consideration the degree to which the thiazide increases the serum urate level, whether this increase can be managed without overly complicating the patient's hypouricemic therapy, and, most importantly, what effect switching to another drug will have on the control of the patient's hypertension. No study has directly addressed this issue.

My practice in most patients, for reasons I explain below, is to use a thiazide if it helps to control the blood pressure and to adjust the dose of the hypouricemic therapy as needed to reduce the serum urate to the desired level.

THIAZIDES REMAIN IMPORTANT IN ANTIHYPERTENSIVE THERAPY

Many patients with gout also have hypertension, perhaps due in part to the same hyperuricemia that caused their gouty arthritis. It is well documented that thiazide diuretics can raise the serum urate level.[1] In some studies[2] (but not all[3]), patients using thiazides had a higher incidence of gouty arthritis. Thus, it is reasonable to ask if we should avoid thiazides in patients with coexistent gout and hypertension.

Many hypertensive patients fail to reach their target blood pressures (although with the "looser" recommendations in the latest guidelines,[4] we may appear to be doing a better job). The reasons for failing to reach target pressures are complex and many: physicians may simply not be aggressive enough in pursuing a target blood pressure; patients cannot tolerate the drugs or cannot afford the drugs; and many patients need two or more antihypertensive drugs to achieve adequate control. Thiazides are cheap and effective[5] and work synergistically with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.[6]

Thus, in many patients, avoiding or discontinuing a thiazide may inhibit our ability to control their hypertension, which is a key contributor to cardiovascular events and chronic kidney injury in patients with gout. Since other diuretics (eg, loop diuretics, which can lower blood pressure but often require split doses) also raise the serum urate level, switching to one of them will not eliminate concern over hyperuricemia.

Thiazides and serum urate

Thiazides slightly increase the serum urate level and in a dose-dependent manner. At the doses commonly used in treating hypertension (12.5 or 25 mg once a day), hydrochlorothiazide increases the serum urate level by 0.8 mg/dL or less in patients with normal renal function, as shown in a number of older

In most cases, I continue the thiazide and adjust the hypouricemic therapy if necessary to reach the target serum uric acid level

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hypertension treatment trials and in a recent prospective study.[1] The effect of chlorthalidone is similar.

In patients with chronic gout treated with a xanthine oxidase inhibitor (allopurinol or febuxostat) to lower the serum urate to the American College of Rheumatology's recommended target level[7] of less than 6.0 mg/dL (or < 5 mg/dL in the British Rheumatology guidelines), this small elevation in serum urate is unlikely to negate the clinical efficacy of these drugs when dosing is optimized. Small studies have demonstrated a clinically insignificant pharmacodynamic interaction between thiazides and xanthine oxidase inhibitors.[8,9] When I add a thiazide to a patient's regimen, I do not usually need to increase the dose of allopurinol significantly to keep the serum urate level below the desired target.

Switch antihypertensive therapy

Occasionally, in a patient with chronic gout and mild hypertension who has a serum urate level marginally above the estimated precipitation threshold of 6.7 mg/dL, it is reasonable to simply switch the thiazide to another antihypertensive, such as losartan. Losartan is a weak uricosuric and can lower the serum urate level slightly, possibly making the addition of another hypouricemic agent unnecessary, while still controlling the blood pressure with a single pill. This decision must be individualized, taking into consideration the efficacy and cost of the alternative antihypertensive drug, as well as the potential but as yet unproven cardiovascular and renal benefits of lowering the serum urate with a more potent hypouricemic to a degree not likely to be attained with losartan alone.

Hydrochlorothiazide 12–25 mg daily increases the serum urate level by ≤ 0.8 mg/dL

Continue thiazide, adjust gout therapy

Discontinuing a thiazide or switching to another antihypertensive drug may increase the cost and decrease the efficacy of hypertensive therapy. Continuing thiazide therapy and, if necessary, adjusting hypouricemic therapy will not worsen the control of the serum urate level or gouty arthritis, and in most patients will not complicate the management of gout.

ASPIRIN AND HYPERURICEMIA

In answer to a separate but related question, aspirin in low doses for cardioprotection (81 mg daily) also need not be stopped in patients with hyperuricemia or gout in an effort to better control the serum urate level. Low-dose aspirin increases the serum urate level by about 0.3 mg/dL. Since patients with gout have a higher risk of having cardiovascular disease, metabolic syndrome, and chronic kidney disease, many will benefit from low-dose aspirin therapy. ■

REFERENCES

1. **McAdams DeMarco MA, Maynard JW, Baer AN, et al**. Diuretic use, increased serum urate levels, and risk of incident gout in a population-based study of adults with hypertension: the Atherosclerosis Risk in Communities cohort study. Arthritis Rheum 2012; 64:121–129.
2. **Choi HK, Soriano LC, Zhang Y, Rodríguez LA**. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. BMJ 2012; 344:d8190.
3. **Hueskes BA, Roovers EA, Mantel-Teeuwisse AK, Janssens HJ, van de Lisdonk EH, Janssen M**. Use of diuretics and the risk of gouty arthritis: a systematic review. Semin Arthritis Rheum 2012; 41:879–889.
4. **James PA, Oparil S, Carter BL, et al**. 2014 Evidence-based guideline for the management of high blood pressure in adults. Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2013; doi:10.1001/jama 2013.284427
5. **Fuchs FD**. Diuretics: still essential drugs for the management of hypertension. Expert Rev Cardiovasc Ther 2009; 7:591–598.
6. **Sood N, Reinhart KM, Baker WL**. Combination therapy for the management of hypertension: a review of the evidence. Am J Health Syst Pharm 2010; 67:885–894.
7. **Khanna D, Fitzgerald JD, Khanna PP, et al; American College of Rheumatology**. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012; 64:1431–1446.
8. **Löffler W, Landthaler R, de Vries JX, et al**. Interaction of allopurinol and hydrochlorothiazide during prolonged oral administration of both drugs in normal subjects. I. Uric acid kinetics. Clin Investig 1994; 72:1071–1075.
9. **Grabowski B, Khosravan R, Wu JT, Vernillet L, Lademacher C**. Effect of hydrochlorothiazide on the pharmacokinetics and pharmacodynamics of febuxostat, a non-purine selective inhibitor of xanthine oxidase. Br J Clin Pharmacol 2010; 70:57–64.

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