

Hypouricaemia

Fenofibrate and losartan

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Should we take advantage of their uricosuric properties in clinical practice?

The interesting study published in this issue of the journal by Takahashi *et al* sheds light on two drugs, losartan and fenofibrate, which have hypouricaemic properties, in addition to their main therapeutic effects.¹

LOSARTAN

Losartan potassium is an orally active angiotensin II receptor antagonist used for the treatment of hypertension. This product and its long life metabolite E-3174 are potent antagonists at the AT1 receptor. The observation that losartan increases urinary uric acid excretion and reduces serum uric acid level was first made in a pilot study conducted in healthy subjects and published in 1992. Uric acid fractional clearance was mainly increased during the first four hours after drug intake in a time course consistent with a direct effect of the drug. The increase was found to be dose dependent and to persist after seven days of administration.² Angiotensin is known to lower uric acid renal clearance,³ but the uricosuric effect of losartan did not appear to be mediated by angiotensin inhibition: in one study, infusion of E-3174, the active metabolite of losartan, did not modify uric acid excretion, although it efficiently decreased blood pressure.⁴ The early and transient uricosuric action of losartan was therefore attributed mainly to the mother compound. Further suggestions of an effect independent of angiotensin II receptor blockade came from the observation that the uricosuric effect did not vary with a sodium diet⁵ and was not seen with other angiotensin II receptor antagonists.⁶⁻⁸

"Losartan and E-3174 target the urate anion exchanger URAT1"

Losartan and its metabolite E-3174 were recently shown to target the urate anion exchanger URAT1 and inhibit urate uptake by this transporter, thus reducing urate reabsorption from the proximal tubule, which is the main site of URAT1 in the human kidney. The effect was of similar order to that of probenecid.⁹

In most clinical studies, losartan was found to increase the fractional excretion of uric acid. The increase was

moderate, from 3 to 30%,¹⁰ and was not constantly observed.¹¹ In some studies, repeated dosing with losartan resulted in a gradual waning of the uricosuric effect, but moderate reduction of serum uric acid was maintained after 3-4 weeks of treatment.^{11, 12} Losartan was also shown to reduce the increase in serum uric acid caused by hydrochlorothiazide,¹²⁻¹⁴ a finding which might be of clinical significance as long term use of diuretics in hypertensive patients is a well known cause of secondary gout. However, this effect was generally not sufficient to totally normalise uricaemia. Losartan also significantly raises urine pH, an interesting property, not shared by other uricosuric drugs, which might counterbalance the risk of uric acid stone associated with increased uric acid excretion.¹²

FENOFIBRATE

Fenofibrate is a lipid lowering drug, the uricosuric property of which was reported in 1980.^{15, 16} Fenofibrate has been shown to approximately double uric acid clearance and to significantly reduce the serum uric acid level in healthy volunteers,^{15, 17} in diabetic and non-diabetic patients with hyperlipidaemia,^{16, 18, 19} and in patients with gout.²⁰ Lowering of serum uric acid level was constantly seen across studies and was clinically significant, ranging from 20 to 46%. The uricosuric property is not shared by another fibrate, bezafibrate, despite a similar activity in decreasing serum lipids, so that it does not seem to be related to the lipid lowering effect of fibrates.²⁰

COMBINATION WITH CLASSIC URIC ACID LOWERING DRUGS

The study by Takahashi *et al* examines the usefulness of the combination of these two uricosuric drugs with the more classic uric acid lowering drugs in the management of gout.¹ The results, although positive, are a little disappointing, as the observed decreases in serum uric acid were more modest than expected from published data: a mean of 54 $\mu\text{mol/l}$ (15% reduction) was observed with fenofibrate and of 24 or 30 $\mu\text{mol/l}$ (11-15% reduction) with losartan. Previous studies of normal subjects by the same group of investigators showed that both losartan potassium and fenofibrate

increased not only uric acid clearance but also the urinary excretion of oxypurinol, the main active metabolite of allopurinol.^{7, 21} This leads to the concern that the combination of fenofibrate or losartan with allopurinol might lower the hypouricaemic effect of allopurinol. In the study published in this issue of the journal there was no significant difference in the magnitude of the hypouricaemic effect when fenofibrate or losartan was added to allopurinol or benzbromarone, suggesting that the drug interactions were negligible.¹

In a short recent report, urate clearance doubled after addition of fenofibrate to allopurinol,²⁰ whereas it was only increased by 50% in the study by Takahashi *et al*.¹ An explanation for this milder effect may be that in the latter study the drug was given to patients whose uricaemia had been previously effectively reduced by classic hypouricaemic drugs. Serum uric acid level is an important factor of glomerular filtration and urine excretion of uric acid. A smaller amount of filtered urate might have decreased the ability of fenofibrate to inhibit urate tubular reabsorption.

EFFECT ON BLOOD PRESSURE AND CARDIOVASCULAR DISEASE

In the absence of gout, the usefulness of the uricosuric action of losartan and fenofibrate in the management of hypertension and dyslipidaemia, respectively, is still difficult to appreciate. Hyperuricaemia is a common finding in both diseases, and the uricosuric property of these drugs may be seen as beneficial as it would contribute to normalisation of the uricaemia in hypertensive and/or hyperlipidaemic subjects. Essential hypertension is associated with increased renal vascular resistance and tubular sodium reabsorption, which are known to decrease urine uric acid excretion^{22, 23} and explain the high frequency of associated hyperuricaemia. Hypertension and hypertriglyceridaemia are, together with hyperuricaemia, obesity, glucose intolerance, and type 2 diabetes, frequently part of the insulin resistance syndrome. High serum levels of insulin in this syndrome increase sodium reabsorption and decrease uric acid renal excretion.²⁴ Lowering of uricaemia in these patients would be indicated if hyperuricaemia is a risk factor for cardiovascular disease and/or hypertension. Many studies have aimed at determining if hyperuricaemia remains an independent risk factor for cardiovascular disease after controlling for other accepted risk factors. The results have been conflicting. Recent studies, such as the Framingham study,²⁵ found that uric acid is not an independent risk factor, whereas others, such as the NHANES study,²⁶ reached

the opposite conclusion. Faced with this difficulty, most doctors are of the opinion that asymptomatic hyperuricaemia does not deserve any treatment.²⁷ However, this view has been recently challenged by the observation that experimental chronic hyperuricaemia in rats was followed by the development of hypertension, which could be prevented or treated by lowering uricaemia with either allopurinol or benzydaronone.²⁸

“Chronic hyperuricaemia was followed by hypertension preventable by lowering uricaemia”

In this model, the increase in blood pressure was mediated by increased juxtaglomerular renin expression. Hyperuricaemia in rats was subsequently shown to cause glomerulosclerosis and renal arteriopathy, similar to the lesions seen in the kidneys of hypertensive patients.²⁹ These animal data are not directly transposable to humans but suggest that studies should be performed to investigate the effect of uric acid lowering drugs on blood pressure and cardiovascular disease in man.

CONCLUSION

In conclusion, the uricosuric effect of losartan and fenofibrate may be viewed by rheumatologists as an interesting property, which favours the choice of these drugs to treat hypertension and hyperlipidaemia when associated with gout. The uricosuric effect of these drugs should be kept in mind so that steps can be taken to prevent potential uric acid lithiasis, although this side effect does not seem to have been observed thus far. Moreover, it should be emphasised that these drugs are, at present, to be considered as mere adjuvant treatments of hyperuricaemia, as they, especially losartan, have only a mild hypouricaemic effect and have not been registered for the treatment of gout. Whether their use might be interesting in the management of asymptomatic hyperuricaemia associated with dyslipidaemia and/or hypertension remains to be clarified by specific studies.

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