Introduction

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Hyperuricemia is a common side effect of treatment with potent natriuretic agents. Although earlier studies suggested that thiazide diuretic might compete with urate for renal tubular secretion [4], more recent work has indicated that circulatory adjustments play an important role in the pathogenesis of diuretic-induced renal urate retention [11,12]. Most hyperuricemia associated with diuretics are asymptomatic, with gout occurring in less than 10% of the patients [1]. In the great majority, no overt difficulties are caused by chronic elevations of the serum urate.

On the other hand, there is a possibility that uric acid (or, more properly, monosodium urate) could be more toxic than is generally thought. Uric acid, an endproduct of purine metabolism, is not metabolized appreciably in man. Its monosodium salt is sparingly soluble at the pH of extracellular fluid, and can precipitate readily in body tissues. Observations in both gouty and nongouty individuals have demonstrated that the hyperosmotic renal medulla constitutes an especially likely location for urate crystal deposition [3,10,14].

In the Supplement to follow, Tweeddale and Fodor explore the possibility that hyperuricemia could act as a cardiovascular risk factor. They conclude that there is convincing evidence to link hyperuricemia with the development of an elevated blood pressure. On the other hand, a more direct connection between serum urate elevation and the development of vascular disease is elusive. In spite of the excessive cardiovascular morbidity and mortality in untreated gouty patients [13], and in spite of the fact that their platelets may exhibit abnormal activation characteristics and morphologic changes [2], as well as more recent observations that monosodium urate microcrystals can disrupt platelet membranes [8], one still cannot directly

\[ \text{Cf-XX >} \]
\[ \text{CH}^\%\text{COOH} \]
\[ \text{MK-196} \]
\[ 0 \text{Cl} \]
\[ \text{O-Cl}^\%\text{OOH} \]
\[ \text{SKF-62698}^* \text{ticrynafen, tienilic acid} \]
\[ \text{CH}^\%\text{V}^\gamma\text{V} \]
\[\text{ethacrynic acid} \quad \text{CH}_2^\%\%\text{O}-\text{e}^\%\text{COOH} \]

Fig.1. Structure of 3 natriuretic phenoxyacetic acid derivatives. Whereas MK-196 and SKF-62698 (ticrynafen, tienilic acid) exhibit major uricosuric actions, ethacrynic acid does not. link uric acid or urate to the pathogenesis of vascular disease.
This Supplement will be largely devoted to a discussion of two natriuretic diuretics which possess sufficient intrinsic uricosuric activity to prevent hyperuricemia. Other uricosuric diuretic compounds are presently under development, but the two agents discussed in the Supplement have been utilized in man. Both exhibit chemical structural similarities to ethacrynic acid (fig. 1), an agent which promotes chronic urate retention. One of these, an indanyloxyacetic acid (MK-196) effects inhibition of urate reabsorption within the proximal nephron of the rat, but inhibits sodium reabsorption in the loop of Henle, according to observations reviewed in the Supplement by Weinman and his collaborators. The administration of MK-196 to normal man can produce a marked natriuresis, in keeping with its ‘loop’ activity. As will be reported by Emmerson and his colleagues, the uricosuric response elicited by this compound can, under some circumstances, be counteracted – possibly by diuretic-induced volume depletion. Unfortunately, little other information presently is available regarding the action of MK-196 in man. More extensive data regarding renal effects of MK-196 in the chimpanzee have been published [5,6,15].

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The remainder of the Supplement is devoted to a discussion of ticrynafen (tienilic acid)1, a compound which has been studied more intensively in man, and which currently is being marketed in some countries. Although ticrynafen structurally exhibits certain resemblances to MK-196 and ethacrynic acid (fig. 1), its action seems significantly different. In experiments in the dog to be reported by Lemieux and co-workers, as well as by Snow and Maass, ticrynafen is shown to interact with at least one of the renal tubular organic anion transport systems. In fact, it seems likely that the natriuretic and uricosuric actions of ticrynafen depend upon its prior secretion into renal tubule lumens. Studies to be reported by Stote and co-workers indicate that the ticrynafen possesses a natriuretic ‘ceiling’ activity in man similar to that of thiazide-like agents. Furthermore, its site of natriuretic activity appears to reside within the ‘cortical diluting segment’ rather than in the loop of Henle. The uricosuric activity of ticrynafen probably results from widespread inhibition of urate reabsorption. Although precipitation of uric acid and monosodium urate within the urinary tract after ticrynafen might at least theoretically cause crystalluria and a predisposition to calculus formation, recent studies have suggested that this is unlikely because of the ‘diluting’ effect of an increased urinary flow on these crystalloids [7]. Also, a diminished urinary calcium has been reported following prolonged ticrynafen usage in man [9].

Other original clinical studies compare ticrynafen with established therapeutic agents in diseased patients. For instance, Smith and Clements indicate that ticrynafen is as effective a diuretic as hydrochlorothiazide in the treatment of congestive heart failure, but that it does not cause hyperuricemia in that setting. Jain and associates summarize evidence that ticrynafen is at least as effective as probenecid in reducing the serum urate in hyperuricemic patients. Finally, Huang et al. and Bauer and Brooks compare a number of physiologic parameters in individuals receiving ticrynafen and hydrochlorothiazide alternatively. They conclude that effects of these agents are basically similar, except for the final serum urate values obtained. The editors hope that this Supplement will serve to heighten the general level of interest in antihypertensive uricosuric diuretics. Experienced clinicians have not infrequently observed late attacks of gouty arthritis during the prolonged use of the currently available agents. In the future, this complication should be avoidable by employing
This drug is genetically termed ‘ticrynafen’ in North America and carries the WHO-approved designation, ‘tienilic acid’, elsewhere. Investigatively, it sometimes has been termed SKF-62698 and ANP-3624.

the new uricosuric diuretics. Furthermore, the data to be gained from controlled studies utilizing such pharmaco-logic agents eventually may lead to an expansion of our knowledge regarding the biologic significance and degree of importance of chronic hyperuricemia in promoting cardiovascular disease. If these aims are at least partially achieved, we consider our efforts worthwhile.

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References


