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Selectivity of febuxostat, a novel non-purine inhibitor of xanthine oxidase/xanthine dehydrogenase

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Abstract

The purine analogue, allopurinol, has been in clinical use for more than 30 years as an inhibitor of xanthine oxidase (XO) in the treatment of hyperuricemia and gout. As consequences of structural similarities to purine compounds, however, allopurinol, its major active product, oxypurinol, and their respective metabolites inhibit other enzymes involved in purine and pyrimidine metabolism. Febuxostat (TEI-6720, TMX-67) is a potent, non-purine inhibitor of XO, currently under clinical evaluation for the treatment of hyperuricemia and gout. In this study, we investigated the effects of febuxostat on several enzymes in purine and pyrimidine metabolism and characterized the mechanism of febuxostat inhibition of XO activity. Febuxostat displayed potent mixed-type inhibition of the activity of purified bovine milk XO, with Ki and Ki′ values of 0.6 and 3.1 nM respectively, indicating inhibition of both the oxidized and reduced forms of XO. In contrast, at concentrations up to 100 μM, febuxostat had no significant effects on the activities of the following enzymes of purine and pyrimidine metabolism: guanine deaminase, hypoxanthine-guanine phosphoribosyltransferase, purine nucleoside phosphorylase, orotate phosphoribosyltransferase and orotidine-5′-monophosphate decarboxylase. These results demonstrate that

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febuxostat is a potent non-purine, selective inhibitor of XO, and could be useful for the treatment of hyperuricemia and gout.

Keywords: Xanthine oxidase inhibitor; Purine metabolism; Pyrimidine metabolism; Febuxostat

Introduction

Gout is a disorder caused by deposition of monosodium urate crystals in joints and other tissues as a result of extracellular urate supersaturation (Hall et al., 1967; Campion et al., 1987). Hyperuricemia, a concentration of urate in serum above the limit of solubility of this substance (≤ 7.0 mg/dL), is the most important risk factor for the development of gout (Shoji et al., 2004) and occurs as a result of increased uric acid production, impaired renal uric acid excretion, or a combination of these mechanisms. Control of hyperuricemia is most often achieved by reducing uric acid production with an inhibitor of xanthine oxidase (EC 1.1.3.22)/xanthine dehydrogenase (EC 1.1.1.204) (XO), the enzyme catalyzing the two terminal reactions in uric acid synthesis (hypoxanthine→ xanthine→ uric acid), or, less frequently, by employing uricosuric agents to increase renal clearance of uric acid.

To date, the only commercially available XO inhibitor is allopurinol, a purine analogue in clinical use for more than 30 years (Rundles et al., 1963). Allopurinol is metabolized extensively, both by XO (to the active enzyme inhibitor, oxypurinol), and by the phosphoribosyltransferases, hypoxanthine-guanine phopshoribosyltransferase (HGPRT; EC 2.4.2.8)) and orotate phosphoribosyltransferase (OPRT; EC 2.4.2.10), to form nucleotide analogues. Not surprisingly, given the structure similarities to natural purines and pyrimidines, allopurinol, oxypurinol and their nucleotide or nucleoside derivatives inhibit additional enzymes involved in purine and pyrimidine metabolism, including purine nucleoside phosphorylase (PNP; EC 2.4.2.1) and orotidine-5′-monophosphate decarboxylase (OMPDC; EC 4.1.1.23).

Despite generally acceptable efficacy and safety profiles, very rare but serious adverse reactions of allopurinol administration can occur, including interstitial nephritis, renal failure, hepatotoxicity, vasculitis and an array of skin rashes varying from mild to very severe and life-threatening allopurinol hypersensitivity syndrome(AHS) (Hande et al., 1984; Singer and Wallace, 1986; Sauve et al., 1992; Arellano and Sacristan, 1993). Prompting the suggestion that accumulation and/or metabolic actions of allopurinol, oxypurinol and their nucleotide or nucleoside derivatives other than XO inhibition might account for the greater incidence of severe allopurinol adverse reactions among patients with renal insufficiency, is the fact that elimination of allopurinol and oxypurinol from the body is largely by renal excretion (Elion et al., 1968; Yoshimura, 1994).

Febuxostat, 2-[3-cyano-4- (2-methylpropoxy)phenyl)-4-methylthiazole-5-carboxylic acid (also known as TEI-6720 or TMX-67, Fig. 1) is a non-purine, XO inhibitor (Hasegawa, 1998) currently under clinical evaluation for the treatment of hyperuricemia and gout (Kamatani et al., 2003; Schumacher et al., 2002). We previously reported that febuxostat is a potent, mixed-type inhibitor of bovine milk XO (Ki = 0.7 nM) in vitro and had a potent in vivo hypouricemic effect in rodents (Osada et al., 1993; Horiuchi et al., 1999) and chimpanzees (Komoriya et al., 1993). Whether