A rare case of thrombocytopenia secondary to taking febuxostat

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ABSTRACT

A new and powerful selective xanthine oxidase inhibitor called febuxostat seems to be well tolerated by all patient populations, even those who are allopurinol-sensitive. Thrombocytopenia is an extremely uncommon side effect. The case of a 63-year-old man who presented with sudden thrombocytopenia and was ultimately linked to febuxostat consumption is described below. The case happened in our department.

Introduction

Febuxostat, {TEI-6720, TMX-67, 2-[3-cyano-4-(2-methyl-propoxy) phenyl]-4-methyl-thiazole-5-carboxylic acid}, is a non-purine compound. It is a selective inhibitor of xanthine oxidase (XO) that has been developed for the treatment of hyperuricemia and gout, as it was found to have a potent inhibitory activity for XO/xanthine dehydrogenase (XDH).[1] Febuxostat was shown to inhibit both the oxidized and reduced forms of XO, unlike allopurinol and oxypurinol, each of which binds only to one form of the enzyme.[2] The molecular mechanism of inhibition of XO activity by febuxostat is by high affinity binding to the enzyme in a molecular channel leading to the molybdenum-pterin active site, whereas allopurinol exerts relatively weak competitive inhibition on activity of only the oxidized form of XO.[3] In contrast to allopurinol and oxypurinol, febuxostat does not structurally resemble purines or pyrimidines and has no significant effect on the activities of other enzymes involved in purine and pyrimidine metabolism, which might relate to some of the adverse effects caused by allopurinol and its metabolites.[3] Febuxostat has numerous hydrogen bonds, salt bridges, and hydrophobic interactions with amino acids in the active site and almost completely fills the narrow channel leading to the molybdenum center of the enzyme, which is considered as a structure-based inhibitor, whereas allopurinol and oxypurinol are thought to be mechanism-based inhibitors.[4] The XO inhibitory activity and hypouricemic effect of febuxostat compared to allopurinol have been studied *in vitro* and in a variety of animal models.[5] All these studies demonstrated that febuxostat had a greater potency than allopurinol in reducing serum urate levels and/or allantoin levels (Figure 1).

After oral administration, about 85% of febuxostat is absorbed rapidly with a time (tmax) to reach peak plasma concentrations (Cmax) of approximately 1 hour in healthy human subjects.[6] In a phase I study in which oral febuxostat doses of 40, 70, and 120 mg were given to healthy male and female adults (n=154), Cmax values of 1.53, 3.08, and 4.47 µg/mL occurred at tmax of about 1 hour, with area under the plasma concentration-time curve (area under the curve) values of 4.00, 6.93, and 11.31 µg h/mL, respectively. Febuxostat is highly bound to albumin in blood (~99%) and appears to have a low to medium apparent volume of distribution at a steady state of approximately 0.7 L/kg.[7] The metabolism of febuxostat occurs predominantly in the liver by glucuronidation to produce the acyl-glucuronide metabolite (22-44% of the dose), and to a much lesser extent (2-8%), to produce oxidative metabolites, 67M-1, 67M-2, and 67M-4 by cytochrome P450 enzymes. Approximately 25% to 45% of the drug was excreted in urine mainly as the conjugate with only about 1% to 6% being eliminated as the unchanged drug. An additional 2% to 8% of the dose was excreted as oxidative metabolites, either unchanged or as conjugates.

Febuxostat has been shown to be safe and effective in lowering serum urate according to the available clinical data. Doses of 80 mg of febuxostat are more effective in lowering serum urate than doses of 300 mg of allopurinol. Febuxostat has shown to be well tolerated in long-term

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treatment in patients experiencing hypersensitivity/intolerance to allopurinol.

Dose adjustment does not seem to be necessary in patients with mild to moderate renal/liver insufficiency or advanced age according to data from these particular groups of subjects. The most common adverse reactions reported were abnormal liver function tests, headache, and gastrointestinal symptoms, which were usually mild and transient. Hepatotoxicity was not a feature in animal studies, but whether it becomes a limitation in the clinical use of febuxostat needs to be determined in further studies. As with other urate-lowering therapies, the rapid decrease in serum urate associated with initiation of treatment with febuxostat caused a number of patients to experience acute gout flares. This appeared to be more frequent with the more potent serum urate-lowering effects of higher doses of febuxostat, but this increased incidence of gout attacks tended to decline with ongoing treatment and could be attenuated with concomitant prophylaxis during the initiation of febuxostat therapy. In February 2008, 80 mg and 120 mg of febuxostat film-coated tablets (Adenuric®) were granted marketing authorization by the European Commission for the treatment of chronic hyper-uricemia in conditions in which urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis), which is the first major treatment alternative for gout in more than 40 years (CHMP 2008; Ipsen 2008). A concern about potential serious cardiovascular adverse events was noted in the European Commission statement, but this was not apparent in the published clinical trial reports.[1]

Below, we describe the case of a 63-year-old man hospitalized in our medical department who presented one of the rare cases of complication with the use of febuxostat.

Case report

A 63-year-old man is admitted to our medical department for rectal bleeding. Blood tests performed at the emergency department showed a reduction in hemoglobin values (7.5 g\dl) and a reduction in the number of platelets (78,000). Arterial hypertension and gouty arthropathy were reported in the anamnesis. Home therapy consisted of ramipril (5 mg\die) and febuxostat (80 mg\die). An intolerance to allopurinol was also reported.

The patient underwent a transfusion with a bag of concentrated red blood cells with adequate restoration of hemoglobin levels. The number of platelets, however, always remained around 50,000, despite the arrest of rectal bleeding. The patient also underwent a colonoscopy which showed the presence of diverticula in the descending segment of the colon.

Due to the persistence of constantly decreasing platelet values, the patient underwent an abdominal ultrasound, a search for HCV, HIV, EBV, and other viruses that could be responsible for the thrombocytopenia, and finally an osteomedullary biopsy: all negative results.

As an *ex adiuvantibus* criterion, the patient started steroid therapy, without benefit. He then proceeded to discontinue febuxostat. Within a week there was a reversal of the downward trend in the platelet count and the patient was discharged

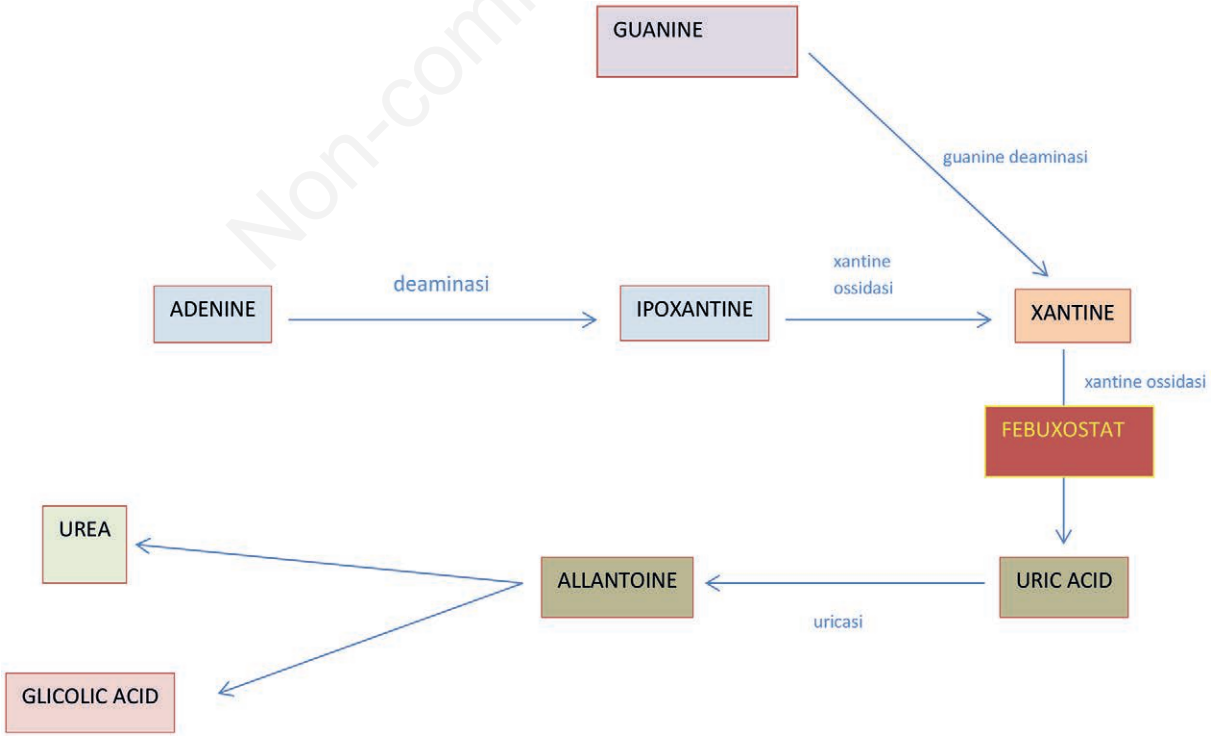

Figure 1. The efficacy of febuxostat in lowering serum urate and/or allantoin levels.

in a stable condition. At a follow-up visit one month later, the platelet values had returned to almost normal.

Discussion

From a structural point of view, febuxostat does not contain analogs purine or pyrimidine, it does not inhibit the enzymes involved in the metabolism of purines or pyrimidines, and for this reason, it has fewer side effects than allopurinol. Unlike allopurinol, febuxostat blocks effectively do not compete the access channel to the active site of the oxidized and reduced forms of XO, thus inhibiting the synthesis of uric acid. Febuxostat is a valid alternative to purinol, compared to which it has greater efficacy in lowering uric acid levels and fewer side effects. The dosage should be increased gradually based on response. Febuxostat has demonstrated an excellent safety profile in patients with renal failure mild-moderate. Thrombocytopenia is included among the rare adverse effects reported in the combined long-term phase III studies and in the post-experience marketing. From this clinical case, we can deduce how iatrogenic lesions must be suspected and are more frequent than is thought in common clinical practice.

Conclusions

This patient underwent numerous instrumental tests, some of which were invasive and difficult to bear. This mass of tests significantly delayed the diagnosis but, in reality, the diagnosis was simple. It should be remembered that medical history and listening to the patient do not replace any technicality which remains important but secondary. This is also important in terms of saving healthcare costs.

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