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The teratogenicity of allopurinol: A comprehensive review of animal and human studies

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ABSTRACT

Allopurinol is widely used in the management of multiple disorders including gout, kidney stones and inflammatory bowel disease. Despite of long-term experience, its safety in pregnancy has been debated due to reports on possible teratogenicity. We aimed to review the literature on the safety of allopurinol in pregnancy and offspring. In animals, allopurinol induced species-specific reproductive toxicity. In humans, a total of 53 allopurinol exposed infants were reported in the literature. Major congenital malformations were reported in two cases with a comparable pattern of multiple abnormalities. Five other infants had minor birth defects. In conclusion, the association between allopurinol and teratogenicity appears to be weak and limited to two reports with uncertain causality. However, the available data are insufficient to make a certain judgement, and as allopurinol treatment evolves, report and prospective follow-up of all exposed infants (*i.e.* deviant and normal cases) should be encouraged.

1. Introduction

Allopurinol is a purine analogue and an anti-oxidative drug, used in the management of multiple disorders, with still rising medical purposes [1]. For over 50 years, allopurinol has been used in the treatment of gout and related hyperuremic conditions such as kidney stones and tumor lysis syndrome [2]. Furthermore, allopurinol is used to treat particular protozoan infections such as Leishmaniasis and *Trypanosoma cruzi* [3,4]. In recent times, allopurinol is being applied in the management of patients with inflammatory bowel disease and autoimmune hepatitis as well, in order to optimize immunomodulating therapy with thiopurines [5,6]. By combining allopurinol with low-dose azathioprine or mercaptopurine, the metabolism of thiopurines advantageously alters leading to increased efficacy and decreased toxicity of thiopurine-derivatives (Fig. 1) [7]. Moreover, allopurinol showed potential benefits in the field of cardiovascular and reproductive medicine. In higher doses, allopurinol scavenges free radicals, which increasingly arise during reperfusion injury [8]. It appears that allopurinol improves endothelial dysfunction and exercise capacity in patients with ischemic heart diseases, and has neuroprotective properties which are valuable in preventing damage after birth asphyxia [9,10].

Allopurinol was developed in the early 1950's by Gertrude Elion and her collaborators during their journey to discover antileukemic drugs (*e.g.* thioguanine, mercaptopurine and azathioprine) [11]. Beside their search for a cure for leukemia, the discoverers aimed at developing a compound that inhibits xanthine oxidase, an enzyme responsible for oxidative stress and uric acid. Multiple compounds were identified eventually including the chemical compound of allopurinol (*i.e.* 4-hydroxypyrazolo(3,4-d)pyrimidine), which was an inhibitor as well as a substrate for xanthine oxidase. In long-term studies, the efficacy and safety of allopurinol in the treatment of hyperuremic conditions, and subsequently other diseases such as inflammatory bowel disease, were observed [12].

During the development of more recent drugs, pregnancy exposure registries are established, but such safety data on many old drugs are lacking. Despite of long-term experience with allopurinol, its safety-profile in pregnancy remains unclarified and has been debated [13–15]. Especially since allopurinol use is increasing in patients of childbearing age such as in inflammatory bowel disease, a condition that mainly affects young adults [5,6,16]. In the literature, both reproductive toxicity and safety of this drug have been broached. On a biochemical level, allopurinol influences more than xanthine oxidase activity and is

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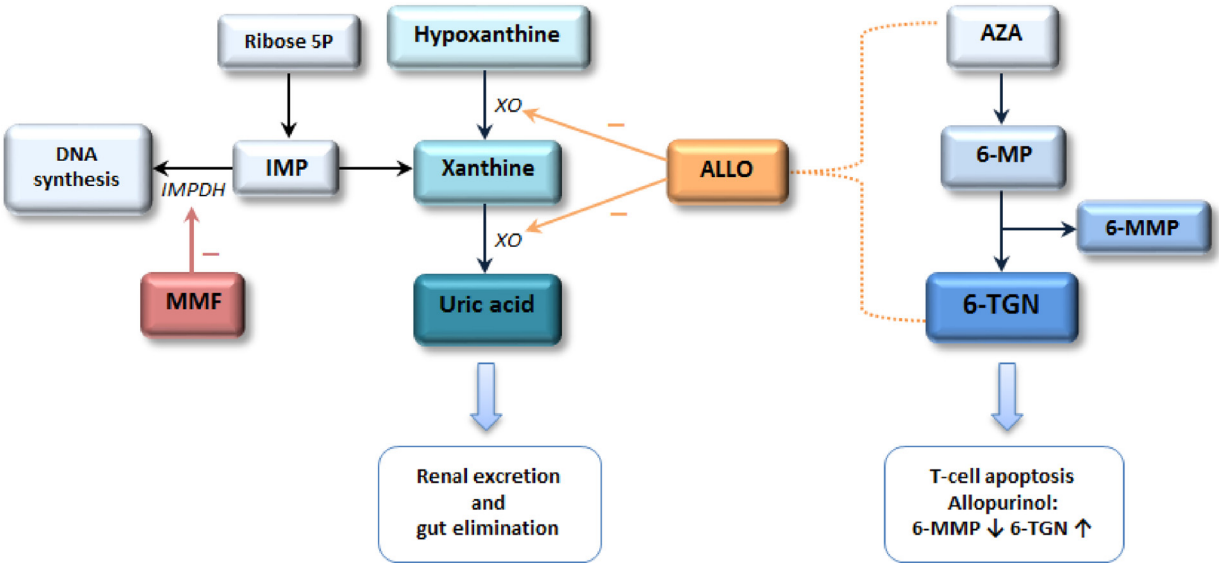

Fig. 1. Simplified schematic representation of allopurinol interaction in purine degradation (left) and thiopurine metabolism (right).
Legend: Abbreviations: MMF: mycophenolate mofetil: IMPDH: inosine monophosphate dehydrogenase; IMP: inosine monophosphate; Ribose-5P: ribose 5-phosphate; XO: xanthine oxidase; ALLO: allopurinol; AZA: azathioprine; 6-MP: 6-mercaptopurine; 6-MMP: 6-methylmercaptopurine; 6-TGN: 6-thioguaninenucleotides.
Left: In the literature, allopurinol has been compared to mycophenolate mofetil, an antimetabolite that selectively inhibits IMPDH activity and has teratogenic properties. Considering that both mycophenolate and allopurinol interact in the purine metabolism, it is speculated that allopurinol may also induce similar teratogenicity. This association, however, is questionable considering that both drugs inhibit different key enzymes that operate in different stages of purine metabolism.
Right: In a subset of patients, co-administration of allopurinol with azathioprine or 6-mercaptopurine preferably shunts thiopurine metabolism towards increased active 6-TGN production, with reduction of toxic 6-MMP levels.

a structural analogue of purines and pyrimidines, theoretically suggesting that it could interfere in the synthesis of nucleotides (in the germ cells or the fetus) [1]. In cytogenetic studies, however, deleterious effects of allopurinol on DNA synthesis were not observed at any stage of the cell cycle [12]. The Food and Drug Administration (FDA) classified allopurinol as a category C drug, meaning that reproductive toxicity in animals has been described, but data in humans are limited and potential benefits may outweigh possible risks. According to online teratogen databases, such as Developmental and Reproductive Toxicology Database (DART) and Teratogen Information System (TERIS), the teratogenic risk of allopurinol is undetermined based on very limited data.

Active chronic diseases are associated with poor pregnancy and birth outcomes, highlighting the importance of disease control prior to and during pregnancy [17]. Therefore, it is important to provide patients who wish to conceive with adequate information, including overviews of published experience, on drugs needed to manage underlying diseases. The purpose of this review was to summarize and critically review the available data on the risk of allopurinol exposure in offspring.

2. Allopurinol in animals

In various animal species, the placental transfer of allopurinol was evaluated in order to study its potential in the management of birth asphyxia when administered maternally [18–21]. In both rodents and large mammals (*e.g.* sows and sheep), allopurinol crossed the placenta and led to therapeutic plasma levels and suppression of xanthine oxidase activity in the exposed fetus. No adverse outcomes of allopurinol exposure in the third trimester were detected, and allopurinol appeared to reduce brain injury after asphyxia in the long-term in animals [22,23].

The reproductive toxicity of allopurinol has been evaluated in several experimental animal studies. In the European public assessment report (EPAR) of allopurinol, it has been described that high oral doses of allopurinol up to 100 mg/kg/day in mice, 150 mg/kg/day in rabbits and 200 mg/kg/day in rats during days 8–16 of gestation did not induce teratogenic effects [24]. In one study in mice exposed to intraperitoneal allopurinol (in doses of 50 or 100 mg/kg) on day 10 or 13 of gestation, fetal abnormalities such as cleft and lip palate and skeletal malformations were observed [25]. In a similar study in rats, doses up to 120 mg/kg of allopurinol did not produce teratogenic effects or fetal death in exposed offspring [26].

Allopurinol appeared to have variable effects on ovulation in different animal species, depending on the extent of xanthine oxidase activity during the entire ovulation process. In rats, allopurinol (100 mg/kg) did not adversely affect ovulation, indicating that xanthine oxidase activity is not a major driver in the ovulation in this species [27]. In rabbits, allopurinol in lower dosages (50 mg/kg) inhibited ovulation and early embryonic development, supporting the possibility of increased xanthine oxidase activity during the ovulation of these animals [28]. In another early report, ovulation in rabbits remained unaffected after allopurinol administration (100 mg/kg) [29]. There are no data on the effects of allopurinol on semen quality in animal species.

Last, Spezia et al. studied the role of hepatic biotransformation in the reproductive toxicity of allopurinol, using a specific exogenous rat and human hepatic enzyme mix (*i.e.* S9) [30]. Rats were exposed to allopurinol (at concentrations ranging from 0.33 to 1.83 mmol), either in the absence or presence of rat or human S9. Fetuses that died in utero were not examined for malformations. Allopurinol induced fetal death without any S9 or when it was combined with rat S9. With human S9, allopurinol induced congenital abnormalities (33% at concentrations of 0.33 mmol, 67% at 0.66 mmol, 20% at 0.99 mmol and 30% at 1.32 mmol), especially concerning the brain and neural tube. The researchers concluded that conflicting outcomes on allopurinol-induced teratogenicity in different animal species might be a consequence of variation in biotransforming reactions, such as in cytochrome P450 enzyme expression [30].