Toxicology Letters 198 (2010) 106–111

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Mini review

Are azole fungicides a teratogenic risk for human conceptus?

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ARTICLE INFO

Article history:
Received 21 May 2010
Received in revised form 2 July 2010
Accepted 6 July 2010
Available online 13 July 2010

Keywords:
Azole fungicides
Birth defects
Azoles
Fungicides
Birth defects
Pregnancy
Mechanisms

ABSTRACT

Azole fungicides are widely used in agriculture and in human mycosis. Their antifungal activity is based on their ability to inhibit CYP51, a key enzyme in the formation of fungal wall. Several azole fungicides tested in laboratory animals have been found to possess a common teratogenic potential to induce facial, axial skeleton, and limb defects. The mechanism of the teratogenic effect has been hypothesized to be related to the capability of these substances to alter embryonic retinoic acid catabolism. Although a number of human epidemiological studies were unable to demonstrate a definite relationship between azole exposure during pregnancy and birth defects, some case reports indicate a possible teratogenic effect of high doses of azoles in humans. Because of their common mechanism of action, azole fungicides should be regarded with caution for use in pregnant women.

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Contents

1. Introduction

Azole agents (triazole- and imidazole-derivatives) are a family of chemicals with antimycotic property. For this reason they are widely used as antifungal agents in agriculture and in human mycosis. More than 20 different active compounds are on the market for medical use against superficial and deep mycosis for oral, topical, vaginal, or systemic treatment of candidiasis and coccidioidal or cryptococcal meningitis, even during pregnancy (King et al., 1998; Jeu et al., 2003; Kale and Johnson, 2005). Dosing regimen of 100–200 mg/day is usually suggested, but larger doses (800–1200 mg/day, i.v.) are recommended for candidaemia and meningitis. About 40 different azole agrochemicals are sold worldwide against mildews and rust of cereal grains, fruits, vegetables and ornamentals accounting for several thousand tons per year.

Azole antifungals act by competitive inhibition of CYP51 (lanosterol 14α–demethylase) which is a key enzyme for sterol biosynthesis in fungi. Selective inhibition of CYP51 would cause depletion of ergosterol and accumulation of lanosterol and other 14-methylsterols, resulting in alterations of fungal wall and in the growth inhibition of fungal cells (Berg et al., 1984; Van den Bossche, 1985). The mechanism seems to be related to the interaction of the N-4 nitrogen atom with the central iron atom in porphyrin system of CYP51. The inhibitory potency of these compounds is not limited to fungi. Inhibition has been observed in a number of mammalian cytochrome P450-dependent activities, including hepatic microsomial enzymes (Sheets and Mason, 1984), accounting for the possible interference of azoles with the metabolism of other drugs (Blum et al., 1991; Kantola et al., 2000). For example, a concentration-dependent inhibition of CYP26, involved in the catabolism of all-trans-retinoic acid has been reported *in vitro* and in patients with promyelocytic leukemia (Vanier et al., 2003; Schwartz et al., 1995).

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doi:10.1016/j.toxlet.2010.07.005

In light of the wide use of this class of agents and, as a consequence, the possible exposure during pregnancy, there is an urgent need for an adequate characterization of their toxic effects on human conceptuses. The aim of this paper is to examine the human and experimental data on developmental toxic effects related to exposure to azole fungicides and to try to draw a meaningful conclusion on the safety of use of these compounds during pregnancy. We also discuss their mechanism(s) of action.

2. Animal studies

The developmental effects of some azole fungicides have been tested in experimental animals using both *in vivo* and *in vitro* approaches. Female CD-1 mice were treated by gavage with 700 mg/kg of Fluconazole on days 8, 9, 10, 11, or 12 of gestation. Day 10 was identified as the phase of maximal sensitivity for induction of cleft palate (50%). This malformation was observed after treatment in the other gestation days also, but with lower frequency. Fetuses exposed on day 8 of gestation revealed abnormalities of the middle ear ossicles (15%); a reduced humeral length was observed in 22% of fetuses that were exposed on gestation day 10. A dose–response relationship was investigated only on day 10 (the day of maximal susceptibility to cleft palate). Fluconazole operated under a strict dose-dependent mechanism with a LOAEL of 175 mg/kg (only 7.6% of cleft palate) (Tiboni and Giampietro, 2005).

Pregnant CD-1 mice were treated on gestation days 8, 9, 10, 11, or 12 with 50, 150 or 250 mg/kg of Itraconazole (gavage). Cleft palate was recorded after treatment in all experimental days with a peak of incidence after treatment on day 10 (about 10% both with 150 or 250 mg/kg); only the highest dose was able to affect limb development (brachydactily and syndactily) and to induce axial skeletal defects (20% with exposure on day 8 and 12% after exposure on day 9) (Tiboni et al., 2006).

Farag and Ibrahim (2007) administered 10, 20, or 40 mg/kg/day of the agrochemical Flusilazole to CD-1 female mice on days 6–15 of gestation. Signs of maternal toxicity (reduction of weight gain and food consumption) were observed at the highest doses. The only observed malformations were at the level of the axial skeleton and limbs at the high and mid level exposure.

Menegola et al. (2005a) treated female CD-1 mice on day 8 of gestation with 300 mg/kg of the agrochemical Triadimefon: 86% of the fetuses presented severe craniofacial defects (middle ear ossicles 47%, timpanic ring 82%, squamosal and zygomatic bones, 52% and 42% respectively), 87% of fetuses showed axial skeletal defects, and 23% of fetuses had cleft palate. Triadimefon (500 mg/kg) was administered to CD-1 mouse on days 8, 9, 10, 11, or 12 of gestation. Cleft palate and axial skeletal defects were induced at every treatment time point, with peaks of sensitivity to cleft palate on gestation days 8 and 12 (Menegola et al., 2009).

When 60 mg/kg of Miconazole was administered to pregnant mice on days 8, 9 or 10 of gestation, an increase of axial skeletal defects (5.6%) was recorded only after treatment on day 8. On the contrary, the administration of the same dose of metronidazole on the same days was unable to induce skeletal malformations. Coadministration of the two azoles on day 8 or 9 of gestation at the same dose produced a synergistic effect with about 26% of fetuses with axial skeletal defects (Tiboni et al., 2008).

The administration of 80 mg/kg/day of Ketoconazole to female rats on days 6–15 of gestation induced some signs of maternal toxicity (reduction of body weight gain and food consumption) and about 60% of cleft palate in fetuses, reduced ossification of skull bones, and axial skeletal defects (Amaral and Nunes, 2008).

Cyproconazole administered daily to female Wistar rats from the 6th to the 16th day of gestation by gavage (20, 50, 75, 100 mg/kg/day) induced a dramatic increase of resorptions at the highest dose. A dose-related increase in embryolethality and cleft palate was observed at all dose levels with dose-dependency. A dose-dependent reduction of fetal body weight was also recorded (Machera, 1995).

Administration of 250 or 500 mg/kg of triadimefon to pregnant CD:Crl rats on day 9.5 of gestation resulted at term in a dose-related increased frequency of craniofacial and axial skeleton malformations (Di Renzo et al., 2006)

The postimplantation whole embryo culture (WEC) system allows the growth *in vitro* of rodent embryos during the period of organogenesis (New, 1978; Giavini et al., 1991). Several WEC studies using rat or mouse embryos have shown that azoles (Triadimefon, Triadimenol, Fluconazole, Flusilazole, Ketoconazole, Enilconazole) are able to produce specific malformations at the level of the branchial arches: hypoplasia of the first and second branchial arch,and fusion of the branchial arches (Tiboni, 1993; Menegola et al., 2000, 2001, 2006). The branchial arch apparatus is a transient structure from which the majority of the craniofacial skeletal structures and musculature are derived.

Congenital malformations similar to those obtained in laboratory mammals have also been described in frog (*Xenopus laevis*), and in ascidian embryos. Groppelli et al. (2005) studied the effects of Triadimefon and Triadimenol on development of *Xenopus* embryos: teratogenic effects were observed, after exposure at the neural stage, at the level of cartilages and muscles derived from the 1st and 2nd branchial arches. The exposure of *Xenopus* embryos to 2.73 μM concentrations and higher of Triadimefon during the neurulation phase resulted in malformations of branchial arch derived cartilages (Papis et al., 2007). Imazalil and Triadimefon were able to alter the anterior structures (papillary nerves and the anterior central nervous system) of the embryos of the ascidia *Phallusia mammillata* with a teratogenic concentration 50 (TC_{50}) of 0.67 and 29.5 μM, respectively (Pennati et al., 2006). The same malformations were described in embryos of the ascidia *Ciona intestinalis* exposed to Imazalil with a TC_{50} of 0.73 μM (Zega et al., 2009).

In summary, the studies carried out in rodents with different azole fungicides revealed their teratogenic potential. The described malformations are at the level of the facial structures (including cleft palate), axial skeleton, and limbs. Although the malformations were observed at very high doses of fungicides, the types of malformations seem to indicate a direct effect of these molecules on the developing embryos. Furthermore, several azoles tested *in vitro* on WEC induced a similar pattern of abnormalities, mainly those of the branchial arches. Finally, the effects observed in frog and ascidian embryos, are indicative of a common mechanism(s) of action for the teratogenic effects induced by azole derivatives.

3. Human studies

The hazard for the developing human conceptus exposed *in utero* to azole fungicides has been investigated using different methodological approaches.

In a population based case-control study, Czeizel et al. (2003) concluded that treatment with Econazole (vaginal suppository of 150 mg/day) during the first trimester or during the entire pregnancy does not indicate any teratogenic risk for the fetus. Using a similar epidemiologic approach, Czeizel et al. (2004) excluded an increased risk of congenital malformations related to the use of Miconazole as cream (300 mg/day) for vulvovaginitis. The same group (Kazy et al., 2005a) was unable to demonstrate an increased risk for congenital malformations in infants from mothers who received oral tablets (200 mg, 1 or 2 per day) of Ketoconazole during the second and third month of gestation. In a retrospective study on 234 women who received a single 50 mg/day dose of Fluconazole during the first trimester of gestation, Jick (1999) was unable to demonstrate an increased risk of congenital malformations. Mastroiacovo et al. (1996) in a prospective cohort study of

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