

Fluconazole use during breastfeeding

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Abstract

Question I have a patient with persistent breast and nipple thrush. Other therapies have failed, so I have decided to treat her with a loading dose of 400 mg of oral fluconazole followed by 100 mg twice daily for at least 2 weeks. Is there any need for her to interrupt breastfeeding during this treatment?

Answer Available data regarding fluconazole use during breastfeeding are reassuring. Fluconazole is also used in the treatment of fungal diseases in infants and has a good safety profile. Therefore, there is no need to interrupt breastfeeding when a mother is treated with fluconazole.

Exposition au fluconazole durant la grossesse

Résumé

Question Une de mes patientes souffre d'une candidose aux seins et aux mamelons. D'autres thérapies ont échoué et j'ai donc décidé de la traiter avec une dose d'attaque de 400 mg de fluconazole par voie orale, suivie de 100 mg 2 fois par jour pendant au moins 2 semaines. Est-il nécessaire qu'elle interrompe l'allaitement durant ce traitement?

Réponse Les données disponibles concernant l'utilisation du fluconazole durant l'allaitement sont rassurantes. Le fluconazole est aussi utilisé dans le traitement des maladies fongiques chez les nourrissons et a un bon profil d'innocuité. Par conséquent, il n'est pas nécessaire que la mère cesse d'allaiter pendant son traitement au fluconazole.

Fluconazole is a triazole antifungal agent that inhibits the fungal cytochrome P450-dependent enzyme lanosterol 14 α -demethylase, disrupts the fungal cell membrane, and impairs cell replication.^{1,2} Fluconazole has high oral bioavailability (>90%), low protein binding, and good tissue penetration.^{1,2} Its terminal elimination half-life is approximately 30 hours and it is mostly (approximately 80%) excreted unchanged in urine. Fluconazole has high in vivo and in vitro activity against most *Candida* strains and is used in a variety of doses (usually 1 to 12 mg/kg daily in children and 100 to 400 mg daily in adults) and durations (days to months) for different types of fungal infection in preterm infants, neonates, children, and adults.¹

The relative infant dose (RID) is an important parameter for predicting the safety of taking medications while breastfeeding. It is calculated by dividing the dose transferred to the infant via the milk (mg/kg daily) by the mother's weight-adjusted dose (mg/kg daily). An RID of less than 10% is generally considered safe for breastfeeding.³

Human data in breastfeeding

Fluconazole has been reported to be excreted in human milk. Schilling et al describe a woman who was taking 200 mg of oral fluconazole per day for 30 days.

Milk samples were obtained 8 days post partum (the 18th day of treatment). The maximum level of fluconazole detected in the milk was 4.1 mg/L, measured 2 hours after the dose. The estimated RID calculated with this value was 17%. The fluconazole elimination half-life in breast milk was calculated to be 26.9 hours in this report.⁴

In another report, breast milk concentrations of fluconazole after oral administration of 150 mg were 2.93 μ g/mL, 2.66 μ g/mL, 1.76 μ g/mL, and 0.98 μ g/mL at 2 hours, 5 hours, 24 hours, and 48 hours, respectively. The estimated RID was 17% in this case. The terminal half-life in breast milk was calculated to be 30 hours.⁵

It is important to note that the RIDs calculated in the above studies used the highest level of fluconazole in the breast milk, not the average level; therefore, these are overestimates, as the infant would not be exposed to this amount with each feeding.

Effects reported in breastfed infants

Chetwynd et al described a breastfeeding mother with persistent *Candida* mastitis. After 2 weeks of use and failure of topical nystatin, 200 mg of oral fluconazole per day was added to her treatment regimen. She continued breastfeeding her infant, who at 13 weeks of age also

received 18 mg of oral fluconazole per day for 10 days after positive oral culture results for *Candida albicans*. During the mother's 11-week treatment and the simultaneous treatment of the baby and mother, no adverse events were reported in the infant.⁶

Bodley and Powers reported a case in which a mother took fluconazole (mostly 200 mg daily) for 6 weeks. Liver function tests were ordered for her 9-week-old baby at the end of treatment, and a slight increase in lactate dehydrogenase levels was reported; however, this was not deemed to be of clinical concern.⁷

Moorhead et al followed 96 breastfeeding mothers who were taking oral fluconazole for the treatment of *Candida* mastitis. The women took a mean of 7.3 (range 1 to 29) 150-mg doses of oral fluconazole. The mean age of their babies was 7.2 weeks (range 1 to 42 weeks). Adverse events were reported in 7 babies including flushed cheeks, abdominal pain, possible diarrhea, mucous feces, tiredness, and eczema (which improved with a change in detergent and maternal diet).⁸

Safety of fluconazole in children

In a review by Novelli and Holzel, 562 children (aged 0 to 17 years), most of whom were immunocompromised, were treated with 1 to 12 mg/kg of fluconazole per day for 1 to 20 days. Adverse events were reported in 10.3% of children, with the most common being gastrointestinal (GI) symptoms; however, the treatments for associated diseases in these children might have caused the symptoms. No evidence of substantial hepatotoxicity was recorded, and transient increases in liver enzyme levels occurred in less than 5% of patients.⁹

Schwarze et al concluded that fluconazole was effective and well tolerated in the treatment of 726 children younger than 1 year of age with systemic candidiasis and candidemia.¹⁰

A recent systematic review including 90 studies demonstrated the relative safety of fluconazole use in neonates and other pediatric age groups (birth to 17 years of age). The review included 4209 children, 2354 of whom were preterm neonates. Fluconazole was administered either as prophylaxis (interquartile range [IQR] 3 to 6 mg/kg) or therapeutically (IQR 5 to 6 mg/kg daily). The IQR for the duration of treatment was between 14 and 67 days. The relative risk (RR) of all adverse events in the fluconazole group did not differ significantly when compared with the placebo group (RR=1.30, 95% CI 0.84 to 2.03) and the other antifungal drugs group (RR=1.05, 95% CI 0.62 to 1.80). Hepatotoxicity was the most commonly observed adverse event (37.1%); however, it was not significantly more frequent than in the placebo group (RR=1.36, 95% CI 0.87 to 2.14) or other antifungal group (RR=1.43, 95% CI 0.67 to 3.03). Gastrointestinal findings, such as anorexia, gastritis, dyspepsia, GI upset, nausea, vomiting, diarrhea, and abdominal pain, were the

second most common adverse events; however, these findings were also not significantly different from groups taking placebo or other antifungal drugs.¹¹

Conclusion

Available data suggest that the estimated RID of fluconazole is higher (approximately 17%) than the generally accepted safe threshold of 10%. However, based on the studies discussed above, the dose that the infant is exposed to through breastfeeding (<0.6 mg/kg daily) is lower than the dose used for systemic treatment (1 to 12 mg/kg daily in premature infants and 3 to 12 mg/kg daily in infants)¹ in the pediatric age group, which has been shown to be well tolerated in different studies.⁹⁻¹¹ Therefore, fluconazole is considered compatible with breastfeeding. For typical doses and treatment durations, as in the treatment of vulvovaginal candidiasis or *Candida* mastitis, monitoring the breastfed infant for GI symptoms (nausea, vomiting, diarrhea, etc) is sufficient. If the mother is receiving a high dose or prolonged treatment (weeks to months) for systemic mycosis, monitoring liver function of the infant should be considered.

Competing interests

None declared

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MOTHERISK

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