

Use

Fluconazole is the antifungal agent now very commonly used both to prevent and to treat invasive neonatal *Candida albicans* infection. Resistant strains respond to caspofungin (q.v.).

Pharmacology

Fluconazole is a potent, selective, triazole inhibitor of the fungal enzymes involved in ergosterol synthesis. The drug is reasonably effective against most *Candida* species, other than *C. krusei* and *C. glabrata*. It is also of value in the treatment of Cryptococcal infection (although in this condition treatment needs to be sustained for several weeks). It was first synthesised and patented in 1982. It is water soluble, well absorbed by mouth even in infancy, and largely excreted unchanged in the urine. Penetration into the CSF is good. While high dose systemic exposure (400 mg/day) in the first trimester of pregnancy can produce a constellation of serious fetal abnormalities, there are, as yet, no reports of teratogenicity with a single 150 mg dose in the first trimester, or with topical or oral use later in pregnancy. Fluconazole is probably the best antifungal to use when *Candida* infects the mother's milk ducts during lactation, even though the manufacturers have never endorsed such use, because the baby only gets ~10% of the weight-adjusted maternal dose.

Fluconazole is increasingly used, even in North America, in the treatment of babies with **invasive** (systemic) *Candida albicans* infection. Studies suggest that it is less toxic, and at least as effective as amphotericin B. Liver function tests sometimes show a mild self correcting disturbance, and rashes can occur, but serious drug eruptions have only been seen in immunodeficient patients. The half life is 40–60 hours at birth, but doubles within 2 weeks. It is 20 hours throughout infancy and childhood, but 30 hours in adults. There is no good reason to give amphotericin B as well as high dose fluconazole, but there is evidence that effective treatment of all *Candida* species with by a minimum inhibitory concentration of ≤ 8 $\mu\text{g/ml}$ requires a higher dose than many reference texts currently quote (Wade *et al.*, 2009). *In vitro* modelling also suggests that high dose treatment makes the emergence of resistant strains less likely. Oral fluconazole is widely used to treat **superficial** (topical) infection in adults, and is now starting to be used for this purpose in babies. Prophylactic use has been widely studied in the last ten years (as reviewed in the web site commentary), but some prefer to use nystatin (q.v.) which is not systemically absorbed for, to minimise the risk of fluconazole-resistant strains proliferating.

Diagnosing systemic candidiasis

Systemic candidiasis is difficult to diagnose, but not rare in colonised ill babies. The isolation of *Candida* from blood should never be ignored, especially if the patient has a long line in place, even if the child seems well. Unfortunately, blood cultures may take days to reveal evidence of infection and can be misleadingly negative, but *Candida* has a predilection for the urinary tract and the presence of budding yeasts or hyphae in freshly voided urine should lead to an immediate search for further evidence of infection. A suprapubic tap can be used to collect urine for microscopy and fungal culture to clinch any diagnosis and prove that treatment has been effective. Examination of the blood's buffy coat may show budding yeasts within phagocytic leucocytes. Check the CSF if *Candida* infection is suspected because blood cultures can be negative. Treatment should not necessarily await the outcome of laboratory studies. Congenital infection from ascending vaginal infection can occur. Tracheal colonisation frequently precedes systemic infection. Fungal and bacterial infection can co-exist.

Candida infection of the breast

Give the mother a 150–300 mg loading dose by mouth, and then 100–200 mg once a day for at least ten days. Treat the baby as well, and take steps to minimise the risk of re-infection as outlined in the web commentary.

Prophylactic use in the neonate

Giving 6 mg/kg of fluconazole twice a week is a strategy often used to prevent overt infection in very vulnerable babies (see web commentary). Give 6 mg/kg once every 2 days if prophylaxis is started in babies >6 weeks old.

Treatment in infancy

Systemic infection: Give a 12 mg/kg loading dose slowly IV followed by 6 mg/kg once a day by mouth or IV in babies less than 1–2 weeks old. Give 24 mg/kg and then 12 mg/kg once a day to babies older than this. Double the dosage interval after the first 2 doses if there is renal failure.

Thrush: Give a 6 mg/kg loading dose and then 3 mg/kg once a day by mouth. Many prefer to give nystatin.

Supply

25 ml bottles for IV use containing 2 mg/ml of fluconazole cost £7.30. A 12 mg/kg dose contains 0.92 mmol/kg of sodium. Packs for oral use costing £17 which, when reconstituted, contain 5.6 g/ml of sucrose, provide 35 ml of a solution containing 10 mg/ml. Do not dilute this further, or keep more than 2 weeks after reconstitution. 50 mg, 150 mg and 200 mg capsules for adult use cost between 40p and 80p each.

References

See also the relevant Cochrane reviews ©

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