

FLUCYTOSINE

Use

Flucytosine is now increasingly used, together with amphotericin B (q.v.), to treat respiratory and systemic fungal infection. This combination is used to treat Aspergillosis, Coccidioidomycosis, and Cryptococcosis, and also widely used to treat systemic *Candida* infection, although some prefer to use fluconazole (q.v.) in this situation. Nystatin or miconazole (q.v.) are more appropriately used to treat superficial *Candida* infection.

Pharmacology

Flucytosine (previously called 5 fluorocytosine) is useful in the treatment of systemic infections due to *Candida* species and, because flucytosine penetrates the CSF and amphotericin and flucytosine are synergistic, combined treatment is increasingly advocated. Joint use may also make it possible to use a less toxic dose of amphotericin. While flucytosine has been used successfully on its own in the management of *Candida* renal tract infection, resistant strains have been reported with worrying frequency, and co-treatment with either amphotericin or fluconazole is now universally recommended to make the development of drug resistance less likely. *Candida* species are usually said to be resistant to flucytosine when the minimum inhibitory concentration (MIC) exceeds 60 µg/ml, and to *Cryptococcus* when this MIC exceeds 12.5 µg/ml.

Flucytosine is a fluorinated pyrimidine first developed in 1957 which acts as a competitive inhibitor of uracil metabolism. The drug is well absorbed by mouth and more than 90% is excreted unchanged in the urine. Renal clearance is about three quarters that achieved for creatinine. The half life in the neonatal period is very variable, but usually about 8 hours. The drug is distributed widely through body tissues including the CSF. It is important to watch for leucopenia and thrombocytopenia with sustained use and, because co-treatment with amphotericin and the illness for which treatment is being given can both cause renal function to deteriorate, important to try and measure the trough blood level if the plasma creatinine level rises more than 40 µmol/l. Vomiting and diarrhoea can occur, and reversible liver function changes have been reported. Flucytosine has been given in pregnancy without seeming to cause any apparent harm to the baby, but the risk of teratogenicity cannot be discounted. It is not known whether the drug appears in breast milk.

Diagnosing fungal infection

Notes on the diagnosis of systemic candidiasis appear in the monograph on fluconazole.

Treatment

Neonatal use: Give 50 mg/kg by mouth or IV once every 12 hours for at least 10 days. Start with 50 mg/kg once every 24 hours if there is evidence of renal failure. Any IV infusion is probably best given using a 15 µm in-line filter to trap any possible drug crystals. The manufacturers also recommend slow infusion over at least 20 minutes, although they offer no reason for this recommendation.

Older children: A dose of 50 mg/kg every 6 or 8 hours is normally used in older children. Always check the blood level after 1–2 days if a dose as high as this is used in a young baby.

Blood levels

Marrow toxicity can occur when the blood level exceeds 100 mg/l for any length of time, so it is advisable to check the serum level when the fourth dose is due if renal function could be impaired. Most large hospitals now have access to a laboratory that can measure this, given at least 0.5 ml of whole blood. Peak levels occur a variable time after oral administration in young babies, so it is probably better to monitor the trough level, aiming for a level of 25–40 mg/l (1 mg/l = 7.75 µmol/l) because lower levels are sub-therapeutic.

Supply and administration

250 ml bottles of a 10 mg/ml IV formulation cost £30. This sugar-free IV product can be infused (terminally) into a line containing dextrose or dextrose saline. It can also be given by mouth. A 50 mg/kg dose contains 0.69 mmol/kg of sodium. Prefilled and sealed single dose syringes can be dispensed on request in order to reduce costs, but this and the reserve stock *must* kept at room temperature, and should be protected from light. Indeed crystals of flucytosine may precipitate out if the temperature falls below 18°C (which is why it is wise to use a 15 µm filter during IV administration). If precipitation is suspected, the bottle can be heated to 80°C for 30 minutes to redissolve the precipitate, but decomposition (and 5-fluorouracil formation) occurs with sustained storage at temperatures over 25°C. There is no IV product on the market in America, but an extemporaneous liquid that is stable for 2 weeks at room temperature can be prepared from the 250 mg or 500 mg oral capsules.

References

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