

Use

Amphotericin B is a valuable antibiotic used in the treatment of suspected or proven systemic fungal infection and to treat leishmaniasis (kala-azar). A liposomal formulation should be used if toxicity develops, but routine use is hard to justify, given the cost, since serious toxicity is relatively uncommon in infancy.

Pharmacology

Amphotericin B is a polyene antifungal derived from *Streptomyces nodosum*. It has been widely used to treat aspergillosis, candidiasis, coccidioidomycosis and cryptococcosis since it was first isolated in 1953. It works by binding to a sterol moiety on the surface of the organism, causing cell death by increasing cell membrane permeability. The clinical response does not always correlate with the result of *in vitro* testing. Consider combined treatment with flucytosine (q.v.) when managing systemic fungal infection because amphotericin only penetrates the CSF poorly. Fluconazole (q.v.) on its own may come to be accepted as the treatment of choice for systemic *Candida albicans* infection. Caspofungin (see web commentary) may be tried if systemic infection with a *Candida* organism fails to respond to amphotericin.

Amphotericin is a potentially toxic drug with many common adverse effects including a dose-dependent and dose-limiting impairment of renal function. Drug elimination is poorly understood, unrelated to renal function, and extremely unpredictable in the neonatal period. Significant drug accumulation is thought to occur in the liver ($V_D \sim 4$ l/kg). A low salt intake increases the risk of nephrotoxicity. Anaemia and leucopenia are not uncommon and hypokalaemia may occur. Fever, vomiting and rigor can also occur during or after IV infusion. The risk of anaphylaxis in older patients can be avoided by giving a first 100 microgram/kg IV 'test' dose over 10 minutes 30 minutes before the first full dose of treatment is due. Rapid infusion can cause hyperkalaemia and an arrhythmia, while overdose has occasionally caused death. Over 80% of adults given amphotericin experience some renal impairment, but such problems seem much less common in infancy. Amphotericin crosses the placenta, but does not seem to be toxic or teratogenic to the fetus, so treatment does not need to be withheld during pregnancy. No information is available on the use of amphotericin during lactation.

Diagnosing fungal infection

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

Treatment

Standard formulation: Give 1 mg/kg IV over 4 hours once a day for 7 days, and then 1mg/kg once every 48 hours. Incremental treatment is inappropriate, and a first test dose is not necessary in a neonate. Ensure a sodium intake of at least 4 mmol/kg per day. Treatment is usually continued for 4 weeks.

Liposomal formulation: AmBisome® is the most widely studied product. Start by giving 2 mg/kg IV over 30–60 minutes once a day. Doses of up to 4mg/kg once a day have been used in deep seated neonatal infection involving bone or the CNS without causing any recognisable toxic side effects, and doses of 5 mg/kg once a day are often used in older children with proven infection. Length of treatment has varied widely.

Supply and administration

Ready-to-use prefilled syringes (which should be stored in the dark and used within 48 hours but which do not need to be protected from light during administration) can be dispensed by the pharmacy on request.

Standard formulation: Vials containing 50 mg of dry powder costing £3.40 (which should be stored at 4°C) are also available. Prepare the powder immediately before use by adding 10 ml of sterile water for injection into the vial through a wide bore needle to give a solution containing 5 mg/ml. Shake until the colloidal solution is clear. Then further dilute the drug by adding 1 ml of this colloidal solution to 49 ml of 5% dextrose to give a solution containing 100 micrograms/ml. The batch used *must* have a pH above 4.2, and commercial supplies of dextrose have a pH that may vary between 3.5 and 6.5. One approach is to ensure an adequate pH by always adding buffer (as described in the package insert). The alternative is to measure the pH – easily checked using Whatman pH indicator paper [cat no 2613991] – and only add buffer if this is shown to be necessary. Do not employ a <1 µm filter, expose to bright light, or mix with any other drug.

Liposomal formulation: 50 mg vials of the liposomal preparation (AmBisome) cost £97. Add 12 ml of sterile water for injection BP to obtain a solution containing 4 mg/ml and shake vigorously until the powder is completely dispersed. Take 20 mg (5 ml) from the vial using the 5 µm filter provided, dilute to 20 ml with 5% dextrose to give a solution containing 1 mg/ml, and infuse the prescribed amount over 30–60 minutes.

Compatibility: Do not let either product come into contact with *any* fluid other than 5% dextrose.

References

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