A DRUG: AMPHOTERICIN B OF CLINICAL ADVANTAGES AND IT'S COMPLICATIONS-A REVIEW

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ABSTRACT
Amphotericin B (Amp B) was discovered by some researchers Gold et al., (1956) [1], who were studying a strain of Streptomyces nodosus, an aerobic actinomycete, obtained from the Orinoco River Valley of Venezuela. The antibiotic was isolated by Vandeputte et al., (1956) [2]. In this present review article, we summarized Amp B of clinical advantages and complications.

Keywords: Amphotericin B, History, complications.

INTRODUCTION
Treatment of fungal infections have increased considerably over the last four decades and the pharmacological principles of antifungal therapy are only partially understood [3]. Fungal diseases, both local and intestinal, are common, but systemic fungal infections have become more frequent and important as a consequence of the lowering of host resistance following the increasing use of immunosuppressive drugs and the spread of AIDS. The antifungal agents in current use include some antibiotics as well as synthetic drugs. The antifungal agents are:

- Those employed locally: These include many synthetic drugs. Antibiotics used include nystain and other polyene antibiotics.
- Those used systemically: Amphotericin B (Amp B) selected by the author for the present study is an antibiotic with no antibacterial action, but is highly effective against many yeast like and filamentous fungi and is one of the few antifungal antibiotics that can be given by injection. It is of value in the treatment of deep fungal infections such as Cryptococcus, Histoplasmosis and systemic candidiasis and is given in a dose of 250μg/kg daily by slow intravenous injection, often preceded by a test dose of 1 mg. The injection solution should be freshly prepared and protected from light during administration. The dose is slowly increased up to 1mg/kg daily, but treatment for months may be required, with frequent changes of the injection site, as Amphotericin B is an irritant and may cause local pain and thrombophlebitis.

The dose of Amp B is normally limited to the nephrotoxic effects of the drug and the development of renal insufficiency. The risk of toxicity has recently been reduced with the introduction of two new presentations of Amphotericin for intravenous infusion, Ambisome and Amphocil. Ambisome is a liposome encapsulated preparation of amphotericin, from which the drug is slowly released; Amphocil is a complex of amphotericin with sodium cholestere salt.

HISTORY AND SOURCE OF AMPHOTERICIN B

Chemistry
Amp B is one of a family of some 200 polyene macrolide antibiotics. Those studied to date share the characteristics of four to seven conjugated double bonds, an internal cyclic ester, poor aqueous solubility, substantial toxicity on parenteral administration and a common mechanism of antifungal action. Amp B is a haptaine macrolide, containing seven conjugated double bonds in the transposition of 3-amino-3, 6-dideoxyhexosamine (mycosamine) connected to the main ring by a glycosidic bond. The amphoteric behavior for which the drug is named derives from the presence of a carboxyl group on the main ring and a primary amino group on mycosamine; these groups confer aqueous solubility at extremes of pH. X-ray crystallography has shown the molecule to be rigid and rod-shaped, with the hydrophilic hydroxyl groups of the macrolide ring forming an opposing face to the lipophilic polyenic portion [4] (Fig 1).

Fig 1: Chemical structure of Amphotericin B

Aqueous insolubility of Amp B at neutral pH renders intravenous infusion difficult. Bartner et al., [5] found that Amp B could be solubilized as a colloidal dispersion in deoxycholate. Although this formulation has been in clinical use for more than 30 years, the toxicity of the deoxycholate complex has prompted attempts to develop other formulations. N-acyl derivatives of Amp B or esters of the carboxyl group are generally less active in vitro but can be formulated as water-soluble salts. For example, the methyl ester has been administered intravenously as the hydrochloride, ascorbate or aspartate salt [6]. The amphipathic property of Amp B also permits incorporation of the drug into liposomes. Preliminary clinical experience with two liposomal preparations indicated the neither caused azotemia, but the two differed profoundly in the drug concentrations that were achieved in plasma [7]. Formulations in lipid emulsions and as complexes with cholestere have also been tested; there is a reason to hope for improved formulations of this useful drug.

Current regulations in the United States require that Amp B for intravenous use be at least 75% pure and have no more than 5% amphotericin A, a tetaene. The amount of amphotericin A and of amphotericin X in the commercial product depends upon the strain of Streptomyces used for production and the purification process. Differences in pyrogenicity between lots of the drug and between manufacturers are probably attributable to variable composition and to technical problems in measuring contamination of preparations with endotoxin.

Antifungal Activity
Amp B has useful clinical activity against Candida species, Cryptococcus neoformations, Blastomyces dermatitidis, Histoplasma capsulatum, Torulopsis glabrata, Coccidioides immitis, Paracoccidioides braziliensis, Aspergillus species and the agents of mucormycosis. Methods for determination of susceptibility of fungi to Amp B are still controversial, although efforts at standardization are in progress.
Amp B has limited activity against the protozoa, Leishmania braziliensis and Naegleria fowleri. The drug has no antibacterial activity.
Mechanism of Action

The antifungal activity of Amp B is at least in part dependent on its binding to a sterol moiety, primarily ergosterol, present in the membrane of sensitive fungi. By virtue of their interaction with the sterols of cell membranes, polyenes appear to form pores or channels. The result is an increase in the permeability of the membrane, allowing leakage of a variety of small molecules [8]. Additional mechanisms of action may include oxidative damage to fungal cells, at least in vitro [9], and some capability to enhance cell-mediated immunity in the host [10].

Fungal Resistance

Mutants with decreased susceptibility to Amp B have been isolated from several fungal species by a passage in culture medium containing the drug. Many but not all of these mutants have decreased concentrations of ergosterol in their cell membranes. Some resistant strains have elevated concentrations of precursors of ergosterol with lower affinity for the polyene antibiotics. Isolation from blood or deep tissues of strains with decreased susceptibility has been reported [11], more commonly, species of Candida with decreased susceptibility have been isolated only from the throat, stool or urine, with no evidence that infection with drug-resistant organisms has occurred.

Absorption, Distribution and Excretion

Absorption of Amp B from the gastrointestinal tract is negligible. Repeated daily intravenous infusions to adults of 0.5 mg/kg results in concentrations in plasma of about 1.0 to 1.5 mg/ml at the end of the infusion, which falls to about 0.5 to 1.0 µg/ml 24 hours later [12]. The drug is released from its complex with deoxycholate in the bloodstream and the Amp B that remains in plasma is more than 90% bound to proteins, largely β-lipoprotein. Approximately 2 to 5% of each dose appears in the urine when patients are on daily therapy. Elimination of the drug appears to be unchanged in anephric patients and in patients receiving hemodialysis. In dogs, biliary occlusion results in elevated concentrations of Amp B in blood [13], but hepatic or biliary disease have no known effect on the metabolism of the drug in man. At least a third of the injected doses can be recovered unchanged by methanolic extraction of tissue at autopsy; the highest concentrations are found in liver and spleen, with lesser amounts in kidney and lung [14]. Concentrations of Amp B in fluids from inflamed pleura, peritonitis, synovium and aqueous humor are approximately two-thirds of trough concentrations in plasma. The drug probably crosses the placenta readily [15]. Little Amp B penetrates into the cerebrospinal fluid (CSF), vitreous humor or normal anatomic fluids. Because of extensive binding to tissues, there is a terminal phase of elimination with a half-life of about 15 days.

Preparations, Routes of Administration and Dosage

Amp B (FUNGIZONE) is available for injection. The sterile, lyophilized powder is marketed in vials containing 50 mg of Amp B plus 41 mg of sodium deoxycholate and sodium phosphate buffer. The contents of the vial should be dissolved, with shaking, in 10 ml of sterile water and then added to 5% dextrose in water. Solutions of some electrolytes, acidic solutions or solutions with preservatives should not be used because they cause precipitation of this antifungal agent [16]. If fever and chills in response to administration of the drug are severe, the addition of 0.7 mg/kg of hydrocortisone may alleviate the symptoms in some patients. Meperidine is also effective [17]. Topical preparations of Amp B are also marketed for use.

Opinions vary as to the most effective dosage for administration of Amp B. To a certain extent, the dosage is dependent on the type and severity of the infection. Most physicians agree that a small test dose (1 mg dissolved in 20 ml of 5% dextrose solution) should first be administered intravenously over 20 to 30 minutes. The temperature, pulse, respiratory rate and blood pressure should be recorded every 30 minutes for 4 hours. Fever, chills, hypotension and dyspnea are common. A patient with a severe, rapidly progressing fungal infection, good cardiopulmonary function and a mild reaction to the test dose can immediately receive 0.3 mg/kg of Amp B intravenously over a period of 2 to 4 hours [15]. If the patient has a severe reaction to the test dose or cardiopulmonary impairment, a smaller dose is recommended for example, 0.1 mg/kg or 5 to 10 mg. This dose may then be increased by 5 to 10 mg per day. In severe or fulminant infections, dosage should be escalated rapidly until the patient is receiving 0.5 to 1.0 mg/kg daily. Incremental doses can be given every 6 to 8 hours if reactions in a fragile patient make immediate advancement to full dosage inadvisable. For example, a severe reaction to a 1 mg dose could be followed by 5, 15 and 25 mg given at 8-hour intervals, followed by 40 mg 24 hours later. The recommended maintenance dose for most deep mycoses is 0.4 to 0.6 mg/kg per day, infused over 2 to 4 hours. Adult doses of 10 to 15 mg daily can be sufficient in Candida esophagitis. When used with flucytosine, the daily dose of Amp B is 0.3 mg/kg.

The febrile reactions associated with the administration of Amp B usually subside despite continued use of the drug and the concurrent use of hydrocortisone frequently can be stopped. Amp B may be administered every other day by doubling the recommended daily dose without sacrifice of therapeutic efficacy. The individual dose should not exceed 70 mg in the alternate day regimen, even if the daily dose was greater than 35 mg. There is a greater chance for toxicity and no proof of additional efficacy above this dose. Although this schedule decreases the number of venipunctures and allows more ambulation, the incidence of nephrotoxicity is not reduced and the severity of febrile reactions may increase.

Intrathecal infusion of Amp B is necessary for patients with meningitis caused by Coccidioides. The drug can be injected into the CSF of the lumbar spine, cisterna magna or lateral cerebral ventricle. Irrespective of the site, the treatment is given with 0.05 to 0.1 mg/kg with 0.05 to 0.1 mg/kg additional on a three-times-a-week schedule to 0.5 mg, as tolerance permits. Therapy is then continued on a twice-a-week schedule. Fever and headache are common reactions and may be decreased by administration of 10 to 15 mg of hydrocortisone. Less common but more serious problems attend the use of intrathecal injections; the nature of the problem depends on the injection site chosen. Local injections of Amp B into a joint or peritoneal dialysate fluid commonly produce irritation and pain. Intravascular injection following pars plana vitrectomy has been used successfully for fungal endophthalmitis, but retinal damage can occur.

Unoward Effects

Intravenous administration of Amp B can cause a large number of adverse effects; the two most common are fever and azotemia. Fever and chills are most common at the beginning of therapy; they tend to subside later in the course. The reaction often begins an hour or two after the start of the infusion and lasts 2 to 4 hours. Dyspnea and tachycardia may precede fever. Bronchospasm and true anaphylaxis are rare. The capacity of the drug to release interleukin-1 and tumor necrosis factor from human monocytes and murine macrophages in vitro suggests a mechanism for pyrogenicity. Although administration of Amp B following leukocyte transfusion was, at one time, thought to cause pulmonary infiltrates and hypoxemia, this observation has not been confirmed. Amp B can, however, cause leukocyte aggregation in vitro, an action that could lead to trapping of leukocytes in the pulmonary capillary bed if it occurred in vivo.

Azotemia occurs in 80% of patients who receive Amp B for deep mycoses. Toxicity is dose-dependent, transient and increased by concomitant therapy with other nephrotoxic agents such as aminoglycosides or cyclosporine [18]. Although permanent histologic damage to renal tubules occurs even during short courses, permanent functional defects are uncommon in patients whose renal function was normal prior to treatment unless a total dose in excess of 3 to 4 g is given (to an adult). Renal tubular acidosis and renal wasting of K+ and Mg2+ may also be seen during and for several weeks after therapy. Supplemental K+ is required in a third of patients on prolonged therapy. An increase in intrarenal vascular resistance is the major cause of nephrotoxicity in Amp B treated rats [19]. In patients and experimental animals, loading with sodium chloride has decreased nephrotoxicity, even in the absence of water or salt deprivation. Administration of one liter of saline intravenously on the day that Amp B is to be given has been recommended for adults who are able to tolerate the NaCl load and who are not already receiving that amount in intravenous fluids [20].

Hypochromic, normocytic anemia is usual; the average hematocrit declined to 27% in one study. Decreased production of erythropoietin is the probable mechanism. Anemia reverses slowly following therapy. Headache, nausea, vomiting, malaise, weight loss and phlebitis at peripheral infusion sites are common side effects. Thrombocytopenia or mild leukopenia is observed rarely.

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In cell systems, the most important known mechanisms of Amp B toxicity are an increase in cell membrane permeability to small ions or oxidant-induced membrane damage or both [21]. The fact that this agent produces an increase in membrane permeability and ultimately cell lysis. Possibly related to oxidant-induced membrane damage, suggests that it might be a useful model for the study of cell injury [22].

**THERAPEUTIC USES**

Intravenous administration of Amp B is the treatment of choice for mucormycosis, invasive aspergillosis, extracutaneous sporotrichosis and cryptococcosis. Although imidazoles or triazoles are useful in many patients with blastomycosis, histoplasmosis, coccidioidomycosis and paracoccidioidomycosis, Amp B is preferred when these mycoses are localized or histoplasmosis and is the only effective antifungal drug for the treatment of many fungal infections common side effects include a reaction of fever, chills, headache, an increase in blood pressure and kidney damage. Oral tablets are commercially available in Europe for treating patients with blastomycosis, histoplasmosis, coccidioidomycosis and cryptococcosis. Although imidazoles or triazoles are useful in many patients with blastomycosis, histoplasmosis, coccidioidomycosis and paracoccidioidomycosis, Amp B is preferred when these mycoses are localized or histoplasmosis and is the only effective antifungal drug for the treatment of many fungal infections.

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