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Review

Amphotericin B: side effects and toxicity

Rafael Laniado-Laborín * and Maria Noemí Cabrales-Vargas

Facultad de Medicina Tijuana, Universidad Autónoma de Baja California, Mexico

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ABSTRACT

Amphotericin B (AmB) is a crucial agent in the management of serious systemic fungal infections. In spite of its proven track record, its well-known side effects and toxicity will sometimes require discontinuation of therapy despite a life-threatening systemic fungal infection. The mechanism of action of AmB is based on the binding of the AmB molecule to the fungal cell membrane ergosterol, producing an aggregate that creates a transmembrane channel, allowing the cytoplasmic contents to leak out, leading to cell death. Most of the efforts at improving AmB have been focused on the preparation of AmB with a lipid conjugate.

AmB administration is limited by infusion-related toxicity, an effect postulated to result from proinflammatory cytokine production. The principal acute toxicity of AmB deoxycholate includes nausea, vomiting, rigors, fever, hypertension or hypotension, and hypoxia.

Its principal chronic adverse effect is nephrotoxicity. AmB probably produces renal injury by a variety of mechanisms. Risk factors for AmB nephrotoxicity include male gender, higher average daily dose of AmB ($\geq$35 mg/day), diuretic use, body weight $\geq$90 kg, concomitant use of nephrotoxic drugs, and abnormal baseline renal function. Clinical manifestations of AmB nephrotoxicity include renal insufficiency, hypokalemia, hypomagnesemia, metabolic academia, and polyuria due to nephrogenic diabetes insipidus. Human studies show convincingly that sodium loading in excess of the usual dietary intake notably reduces the incidence and severity of AmB-induced nephrotoxicity.

Anfotericina B: efectos adversos y toxicidad

Palabras clave:
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RESUMEN

La anfotericina B (AmB) es un agente esencial en el tratamiento de las infecciones micóticas sistémicas. A pesar de su demostrada efectividad, sus efectos adversos y toxicidad requieren en ocasiones la interrupción del tratamiento a pesar de la presencia de una infección micótica grave.

El mecanismo de acción de la AmB se basa en la unión del fármaco al ergosterol de la membrana celular del hongo, generando la formación de canales que facilitan la salida del contenido citoplásmico y la consecuente muerte celular. La mayor parte de los esfuerzos para mejorar el perfil de toxicidad de la AmB se han enfocado en la preparación de formulaciones lípicas.

La administración de la AmB se limita por su toxicidad asociada a la perfusión intravenosa. Las manifestaciones mas frecuentes incluyen náuseas, vómitos, escalofríos, fiebre, hipertensión o hipotensión arterial e hipoxia.

Su principal toxicidad crónica se manifiesta a nivel renal. Los factores de riesgo para la nefrotoxicidad incluyen pertenecer al género masculino, una dosis diaria $\geq$35 mg/día, utilización concomitante de diuréticos o drogas nefrotóxicas, peso corporal $\geq$90 kg y una función renal basal anormal. El daño renal se manifiesta como insuficiencia renal, hipocalemia, hipomagnesemia, acidosis metabólica y poliuria secundaria a diabetes insípida. Estudios en humanos han demostrado convincentemente que la administración de solución salina, ya sea por vía oral o parenteral, reduce notablemente la incidencia y severidad del daño renal secundario a AmB.

Amphotericin B (AmB) is a key agent in the management of serious systemic fungal infections. It was introduced in the mid-1950s as the first effective antifungal drug for systemic mycoses[32] and it has been used as the "gold standard" antifungal drug since the1960s.[21,38] AmB is a natural antibiotic belonging to the polyene group, isolated in 1955 from a strain of the actinomycete *Streptomyces nodosus*[18] on soil collected in the Orinoco River region of Venezuela.[32]

Clinical use

AmB has been a mainstay of antifungal therapy for treating disseminated, life-threatening fungal infections. Perhaps the

* Corresponding author.
E-mail address: rafaellaniado@gmail.com (R. Laniado-Laborín).

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major reasons for lasting acceptance of AmB are its broad spectrum of activity and the relatively few examples of mycological resistance to the drug.[18]

In its pure form it has very little solubility in aqueous solutions at physiological pH, requiring complexing with some other agent for clinical administration; the first such agent was sodium deoxycholate. AmB can be administered intravenously, intrathecally, intralesionally, intra-articularly, and infused into surgical sites.[32]

In spite of its proven track record, the requirement for parenteral administration for long periods is inconvenient, frequently necessitating hospitalization and prolonged intravenous (IV) access. Furthermore, its well-known side effects and toxicity will sometimes require discontinuation of therapy despite a life-threatening systemic fungal infection.[2]

Mechanism of action

The mechanism of action of AmB, which is shared in common with other polyenes, is based on the binding of the hydrophobic moiety of the AmB molecule to the fungal cell membrane ergosterol moiety,[10] producing an aggregate that forms transmembrane channels. These defects cause depolarization of the membrane and an increase in membrane permeability to protons and monovalent cations. Intermolecular hydrogen bonding interactions among hydroxyl, carboxyl, and amino groups stabilize the channel in its open form, destroying activity and allowing the cytoplasmic contents to leak out, leading to cell death.[32] AmB also has the capability of binding to the cholesterol of mammalian cell membranes, which is responsible for a major fraction of its toxic potential. Fortunately, more avid binding of AmB to ergosterol than to cholesterol and to ergosterol-containing membranes than to cholesterol-containing membranes has been demonstrated by spectrophotometry. Although some studies question the role of ergosterol binding in the effects of AmB, and no simple relationship between the binding and biological activity of AmB has been found, it is assumed that the basis for the clinical usefulness of AmB is its greater affinity for ergosterol-containing membranes than for cholesterol-containing membranes.[32]

Side effects and toxicity

Multiple attempts have been made to improve on the early preparations of AmB. The principal motivation to the development of additional AmB products is the search for agents that are more efficacious, more tolerable, and less toxic, particularly less nephrotoxic than AmB deoxycholate. One of the earliest was the development of a methyl ester of AmB. This agent, however, proved to have significant neurotoxicity, which caused its further investigation to be abandoned.[32] Most of the efforts at improving AmB over the last 30 years have been focused on the preparation of AmB with a lipid conjugate. Several preparations have been investigated, three of which came to clinical trials and commercialization: AmB colloidal dispersion (ABCD) composed of disk-like structures, AmB lipid complex (Abelcet, formerly ABLC) formed by a concentration of ribbon-like structures of a bilayered membrane, and AmB liposomal (AB-Lip) that consists of unilamellar vesicles containing AmB.[2,13,14,22,28]

It is increasingly apparent that AmB lipid preparations are the new "gold standard" of polyene therapy.[38] Lipid formulations of AmB are better tolerated than AmB deoxycholate and have been used mainly in patients intolerant to conventional AmB or unlikely to tolerate it because of already-altered renal function.[7,28,38,48] High costs, a relative paucity of clinical data, and the existence of alternative antifungal therapies (azoles and echinocandins) explain why lipid formulations have been generally used as second-line therapy.[20]

Acute toxicity of AmB

AmB administration is limited by infusion-related toxicity, an effect postulated to result from proinflammatory cytokine production by innate immune cells. Because AmB is a microbial product, it has been hypothesized that it stimulates immune cells via toll-like receptors in mammalian cells.[42] A study with almost 400 patients[23] showed that more than half of them had at least one infusion-related adverse event.

The principal acute toxicity of AmB deoxycholate, nausea, vomiting, rigors, fever, hypertension/hypotension, and hypoxia do appear to be mitigated by the addition of some of the above-mentioned lipid moieties to the AmB molecule. In a large randomized, double-blind, multicenter trial comparing liposomal AmB with conventional AmB, as empirical antifungal therapy in patients with persistent fever and neutropenia, Walsh et al. analyzed a total of 7025 infusions that were prospectively monitored: 3622 infusions in patients receiving liposomal AmB and 3403 in those receiving conventional AmB. Patients receiving liposomal AmB had fewer infusion-related reactions than did those receiving conventional AmB. When all infusions were analyzed for infusion-related reactions, infusion-related increases in temperature of more than 1 °C occurred in 7.4% of liposomal AmB and 16% of the infusions of conventional AmB ($p<0.001$); infusion-related reactions without fever occurred in 21% of the infusions of liposomal AmB vs. 52% of infusions of conventional AmB ($p<0.001$). Among the documented cardiorespiratory events, there was a significantly lower incidence of hypertension, tachycardia, hypotension, and hypoxia in recipients of liposomal AmB than in recipients of conventional AmB. Flushing reactions occurred almost exclusively in patients treated with liposomal AmB ($p<0.001$). Reflecting the reduced frequency of infusion-related reactions in patients receiving liposomal AmB, these patients were significantly less likely to receive acetaminophen, diphenhydramine, meperidine, hydrocortisone, or lorazepam to prevent such reactions.[50] It soon became apparent, however, that the acute toxicities associated with ABCD were not substantially less than that of the deoxycholate preparation.[32,51]

A more recent multicenter study on acute infusion-related reactions to liposomal AmB reported that acute adverse effects occurred alone or in combination within 1 of 3 symptom complexes: (1) chest pain, dyspnea, and hypoxia; (2) severe abdomen, flank, or leg pain; and (3) flushing and urticaria. Most adverse reactions (86%) occurred within the first 5 min of infusion. All patients experienced rapid resolution of symptoms after IV diphenhydramine administration. The analysis demonstrated an overall frequency of infusion-related reactions of 20%.[40]

A more dangerous side effect of rapid IV infusion is hyperkalemia secondary to shift of potassium from the intracellular compartment,[5] with the potential for the development of fatal cardiac arrhythmias.[25]

AmB deoxycholate has been reported to produce significant cardiac toxicity, with ventricular arrhythmias and bradycardia reported in overdoses in children and in adults with preexisting cardiac disease, even when administered in conventional dosages and infusion rates.[11] Case reports of arrhythmias in patients with normal concentration of potassium and magnesium who were given AmB intravenously suggest that it may be directly cardiotoxic.[24]

Severe hypertension associated with the use of AmB has also been reported in the literature. Of the eight reported cases, six developed severe hypertension within 1 h after administration of