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Review

Amphotericin B: side effects and toxicity

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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

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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

AmB. All cases except one had received a non-lipid-containing preparation. At present, the exact mechanism leading to severe hypertension has not been established.[53]

The neurotoxic potential of AmB is also well documented. Intravenous injection has been associated with hyperthermia, hypotension, confusion, incoherence, delirium, depression, obtundation, psychotic behavior, tremors, convulsions, blurring of vision, loss of hearing, flaccid quadriparesis, with degeneration of the myelin in brachial plexus, akinetic mutism, and diffuse cerebral leukoencephalopathy.[29,49]

Chronic toxicities of AmB

Nephrotoxicity

AmB produces renal injury probably by a variety of mechanisms. Early in therapy there is a significant rise in creatinine. This is secondary to a poorly understood renal vasoconstriction of the afferent arteriole. The deoxycholate moiety may be nephrotoxic and accounts for the differential renal toxicity of AmB deoxycholate as compared with lipid compounds. Additional tubular injury produces hypokalemia and hypomagnesemia and, probably less clinically significant, bicarbonate and amino acid loss. Work in dogs has suggested that AmB nephrotoxicity is caused by enhanced tubuloglomerular feedback. Tubuloglomerular feedback is a normal intrarenal mechanism whereby increased solute delivery to the distal tubule results in afferent arteriolar vasoconstriction. AmB, possibly because of its effects on biologic membranes, increases monovalent ion delivery to the distal tubule, causing afferent arteriolar vasoconstriction, most likely due to local adenosine release. Other mechanisms of AmB nephrotoxicity suggested in the literature are direct toxic effects to the afferent arterioles and tubules and direct renal and systemic vasoconstriction.[2] Within minutes after the IV injection of AmB is begun, renal blood flow is reduced and the production of urine is decreased, despite the maintenance of systemic blood pressure. This renal hypoperfusion has particular impact in the relatively poorly vascularized renal medulla.[29] Eventually there is loss of functioning nephrons and in individuals treated with high doses for prolonged periods, significant renal failure requiring hemodialysis can occur. Nonetheless, it should be noted that significant recovery of renal function can occur and this has been noted since the early days of treatment.[4,9]

Risk factors for AmB deoxycholate 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 (aminoglycosides or cyclosporine), and abnormal baseline renal function.[19] Of note, the incidence of nephrotoxicity rose with increasing number of risk factors, suggesting that alternative therapy might be appropriate in patients with 2 or more risk factors.[8,26] Nephrotoxicity is ultimately the dose-limiting factor in many patients, particularly in situations in which any renal damage is of extreme concern (e.g., in kidney transplant recipients).

Clinical manifestations of AmB nephrotoxicity include renal insufficiency, urinary potassium wasting and hypokalemia, magnesium wasting and hypomagnesemia, metabolic acidemia due to type 1 (or distal) renal tubular acidosis, and polyuria due to nephrogenic diabetes insipidus.[4]

Increases in blood urea nitrogen (BUN) and serum creatinine were originally reported in as many as 80% of patients receiving a full course of AmB.[2] More recent studies have shown that 40–60% of the patients have at least a doubling in serum creatinine after a full course of AmB.[4] Azotemia secondary to AmB is usually considered as reversible, but the incidence of persistent damage has been shown to be dose dependent. Chronic renal failure was observed in 44% of patients receiving more than a total of 4 g of AmB, whereas only 17% of patients receiving less than 4 g had persistent azotemia.[4]

It has been clearly documented that AmB induces renal potassium wasting and can produce substantial potassium deficit. Potassium and magnesium should be routinely monitored during AmB therapy as depletion of these electrolytes can predispose the patient to adverse effects (generalized weakness, ascending paralysis, neurological dysfunction, and life-threatening arrhythmias).[4]

Renal tubular acidosis is a common dose-related manifestation of AmB nephrotoxicity. It is generally reversible within a few months of the end of therapy.

Renal concentrating defect and polyuria is almost invariably present in all patients and occurs early in the course of therapy. It is generally reversible a few months after therapy is discontinued.[4] Animals and humans studies show convincingly that sodium loading in excess of the usual dietary intake notably reduces the incidence and severity of AmB-induced nephrotoxicity and may reverse preexisting nephrotoxicity. The studies, including prospective and controlled trials, have shown the effectiveness of sodium loading as therapy for AmB nephrotoxicity. A recent report proved that high sodium intake ($>$4 meq./kg/day) during AmB therapy was associated with a reduction in the incidence of AmB-induced nephrotoxicity in extremely premature infants with birth weight of less than 1250 g.[47]

Sodium chloride loading in rats, starting 3 days before AmB is given, prevents the rise in serum creatinine levels during long-term AmB administration that occurs in a non-salt-supplemented group. Preservation of renal perfusion and glomerular filtration rate was demonstrated in the saline-fed rats relative to the water-fed rats. Salt loading, however, did not prevent the development of tubular defects, including decreased concentrating ability, diminished acidification, and potassium wasting.[2] The exact mechanism by which this beneficial effect occurs has not been elucidated.

No adverse or toxic reactions to sodium loading in diverse patient groups have been reported. This therapy might be expected to be harmful to patients with preexisting sodium or fluid overload or reduced left ventricular function. Most experience is with the IV infusion of 150 meq. of sodium chloride (1 l of 0.9% sodium chloride solution) per day as either a bolus or continuous infusion, in addition to the usual dietary intake, with an excellent safety profile. This therapy should probably be started at least a day before the AmB regimen is initiated. As mentioned, tubular defects will not be prevented, and thus careful electrolyte management must be assured.[2]

A randomized trial compared the efficacy of an oral rehydration solution vs. an IV saline infusion to prevent nephrotoxicity of AmB. Adult patients with mucosal leishmaniasis treated with AmB also received either 3 l of oral saline solution or 1 l of IV saline solution per day. No significant difference was observed in serum creatinine, creatinine clearance, serum urea, and serum sodium values during treatment, although serum potassium values were lower in the IV saline solution group than in the oral solution group ($p = 0.03$).[17]

In low-risk patients, the use of AmB with prophylactic sodium chloride loading is associated with a small and reversible decrease in renal function.[9]

In the Walsh et al. study,[50] significantly fewer patients receiving liposomal AmB had nephrotoxic effects, as indicated by the doubling or tripling of the serum creatinine level ($p<0.001$) or by peak serum creatinine values above 3.0 mg per deciliter (265 μmol/l); such levels occurred in 12% of those receiving liposomal AmB, as compared with 26% of those receiving conventional AmB ($p<0.001$). This significant reduction in azotemia was also consistent among subgroups of patients receiving concomitant therapy with nephrotoxic agents ($p \leq 0.05$). Moreover, there was a reduction in hypokalemia ($p = 0.02$), as well as a trend toward reduction in hypomagnesemia ($p = 0.12$) in patients receiving liposomal AmB, as compared with those receiving conventional AmB.

A controversial topic regarding AmB is the amelioration of its adverse effects and nephrotoxicity through slower infusion rates. A randomized, controlled, non-blinded, single-centre study in 80 mostly neutropenic patients with refractory fever and suspected or proved invasive fungal infections compared the incidence of adverse effects of AmB administration either by continuous infusion over a period of 24 h or administration over a period of 4 h. Patients in the continuous infusion group had fewer side effects and significantly reduced nephrotoxicity than those in the rapid infusion group. Overall mortality was higher in the rapid infusion cohort than in the continuous infusion group.[48] Two years later, Imhof et al. reported that progressive dose escalation of AmB was well tolerated when administered in continuous infusion and concluded that continuous infusion of AmB escalated to 2.0 mg/kg/day seems not to cause additional impairment of vital organ functions and to be well tolerated by most patients.[31] A retrospective cohort study published in 2004, conducted in hematology patients with fever and neutropenia, including high-risk bone-marrow transplant recipients, compared the incidence of nephrotoxicity of AmB when administered in constant infusion vs. administration over a 4 h period. Renal impairment occurred significantly less frequently in the continuous infusion group (10% vs. 45%, OR 0.14, $p < 0.001$); survival was also significantly higher in the continuous infusion group (95% vs. 79%, OR 5.1, $p = 0.03$).[39] On the contrary, Altmannsberger et al. could not prove any significant advantage of slower infusion rates, as it had been postulated.[1]

Since the vasoconstrictive effects of AmB are clearly calcium dependent, it makes sense to hypothesize that calcium channel antagonists might reduce AmB nephrotoxicity. Indeed, this has been shown conclusively in a rat model using diltiazem for both short- and long-term dosing of AmB. Experience thus far in humans, however, appears to be limited to anecdotal reports, and therefore no firm recommendation can be made with regard to the use of calcium channel blockers.[2]

Other toxicities

Anemia is a side effect in up to 75% of the patients treated with AmB (sometimes with thrombocytopenia). It is the result of direct suppression of erythropoiesis (and platelet formation). Hemolysis from direct interaction between erythrocytes and AmB is unlikely to be an important factor because much higher concentrations than are attained in therapy are necessary for its occurrence. The hematocrit generally stabilizes at 25–30%.[29]

Only a few case reports of AmB-induced hyperbilirubinemia have been documented in the literature, each with different patterns of corresponding abnormalities in liver function tests. The unpredictable nature of this adverse effect warrants monitoring of bilirubin levels and liver function at baseline and potentially during therapy with AmB, regardless of formulation, dosage, or duration of therapy.[37]

Hyperphosphatemia may be an under-recognized problem with administration of liposomal AmB. The phosphate load of liposomal formulations comes from the phospholipid carrier rather than AmB. Liposomal AmB contains 37 mg of inorganic phosphate per 50 mg of AmB administered. Additionally, liposomal AmB is highly protein bound and has slow tissue penetration, which may result in higher phosphate availability.[43] Nevertheless, it has been suggested that the hyperphosphatemia associated with liposomal AmB administration represents pseudohyperphosphatemia because of interference of liposomal AmB with the Synchron LX20 Clinical System (Beckman) analyzer technique.[34]

Hypomagnesemia, usually mild, is a frequent feature of AmB therapy, secondary to renal magnesium wasting. Therefore routine monitoring of the serum magnesium levels is useful during AmB therapy.[6]

There are a few reports of dilated cardiomyopathy associated with AmB therapy, which reverts once treatment is discontinued.[15,33,36]

Hypokalemia secondary to urinary potassium wasting is a frequent adverse effect of AmB therapy; there are reports in the pediatric literature on hypokalemia-associated rhabdomyolysis induced by this drug.[35,41] Correlation between rhabdomyolysis with myoglobinuria and AmB was first reported by Drutz et al. in 1970.[16] Patients on AmB should be checked for this rare yet potentially life-threatening complication.[30]

There is a case report of cutaneous leucocytoclastic vasculitis in which AmB might have presumably been the etiological factor.[12]

It is unclear whether other chronic complications such as anemia, anorexia, and cardiomyopathy are less common with the lipid preparation of AmB than the deoxycholate. What is clear is that all three of the lipid preparations produce less substantial long-term nephrotoxicity.[3,38]

Future alternatives to conventional deoxycholate and lipid AmB

AmB is amphipathic and exhibits low solubility and permeability, resulting in negligible absorption when administered orally. Advances in drug delivery systems have overcome some of the solubility issues that prevent oral bioavailability and new formulations are currently in development.[44] Novel lipid-based AmpB oral formulations in the animal model have provided excellent drug solubilization, drug stability in simulated gastric and intestinal fluids, and antifungal activity without renal toxicity in rats infected with *Aspergillus fumigatus* and *Candida albicans*.[52]

The pharmacokinetics, toxicity, and activity are directly dependent on the type of AmB formulation that is being used. New drug delivery systems such as nanospheres and microspheres can result in higher concentrations of AmB in the liver and spleen and lower concentrations in kidney and lungs, decreasing its toxicity. Furthermore, the administration of these drug delivery systems can enhance the drug accessibility to organs and tissues (e.g., bone marrow) otherwise inaccessible to the free drug.[45]

Incubation of AmB lipid complex (ABLC) with recombinant human apolipoprotein A-I induces solubilization of ABLC by transforming micron-sized phospholipid/AMB assemblies into discrete nanoscale disk-shaped complexes termed nanodisks. Transformation of ABLC into nanodisks seems to preserve the biological activity of AMB as well as the reduced toxicity of the ABLC formulation.[46]

Conclusions and recommendations

When treating a patient with AmB:

- Monitor electrolytes, renal function, magnesium, and phosphates on a regular basis.
- Utilize, if not contraindicated, sodium loading (0.9% sodium chloride solution orally or intravenously) before starting and during treatment.
- Avoid AmB use if the patient has ≥ 2 of the risks factors for nephrotoxicity previously mentioned.

Author's disclosure

Authors have nothing to declare.

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