of a viper bite are significant pain and swelling around the bite area. The pain can be sometimes minimal despite the spreading venom throughout the organism. The most dangerous locations for a bite are head, neck and heavily replete areas. The amount of venom produced by the snake differs and depends on many factors. About 40% of all bites are so called ‘dry bites’ where no venom is present.

FIRST AID FOR SNAKE BITES

Affected limb should be immobilized and the wounded transported to the hospital as soon as possible. According to the latest study, based upon medical records it is self-contradictory:

- Excision - could lead to damage of blood-vessels and nerves!
- Sucking - could infect the wound!
- Stifling - could cause absorption of the venom by the deep bone blood-vessels to arterial circulation increasing the original trauma. Upon release of stifle cardiovascular collapse may occur due to release of toxic matter from the saturated tissue!
- Burning or icing – worsens local damage!

TREATMENT

We manage most cases with unspecified treatment (corticosteroids, vitamins C and K, liquids. Cave salicylic acid (inhibition aggregation of trombocytes). We always apply tetanic antitoxin and if serious symptoms exist we utilize an antiserum (European venom antiserum).

It is necessary to strictly abide by the clinical indication for application of the serum with regards to the possible occurrence of a life threatening anaphylactic reaction!!! (9, 10).

SERUM INDICATIONS:

- intensification and recurrence of the shock;
- serious digestive or neurological symptoms;
- lasting disorders of coagulation;
- extreme local symptoms.

It is of a great risk to apply serum to allergic persons (>30% of the population). Serum should only be provided in a facility with complete resources for dealing with anaphylactic reaction (intensive care).

In the case of a viper bite without any clinical symptoms it is indispensable to observe adults for at least 7 hours and children 24 hours.

REFERENCES


AMPHOTERICIN B, ITS LIPID FORMULATIONS AND CONJUGATES WITH POLYMERS

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SUMMARY

The minireview is focused on novel findings concerning mechanism of action, lipid formulations, polymer conjugates, and structural modifications of amphotericin B.

KEY WORDS: amphotericin B, fungi, systemic mycoses, liposome, lipid formulation, toxicity, prodrugs

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INTRODUCTION

Incidence and prevalence of severe fungal infections have increased over the last decades mainly in the connection with the expanding number of immunocompromised hosts. Amphotericin B (AmB) (Fig. 1), a chiral polyene antibiotic produced by the actinomycete Streptomyces nodosus, is a broad-spectrum antifungal drug used in the treatment of the life-threatening fungal infections.
Mechanism of action is connected with its strong affinity for membrane sterols (higher for ergosterol present in fungal membranes than for cholesterol in mammalian membranes) that results in the formation of AmB-sterol aggregates and subsequently molecular channels across cell membranes. The disruption of osmotic integrity of the membrane leads to the leakage of intracellular ions and molecules, and consequently to fungal cell death. AmB is virtually insoluble in water, and that is why it is not absorbed after oral administration. Conventional AmB for intravenous administration is deoxycholate salt of AmB. Unfortunately, AmB is relatively toxic drug and frequent occurrence of adverse events is a limiting factor for clinical use. AmB shows both acute and chronic toxicity - fever, chills, nausea, vomiting, headache, electrolytic imbalance but also nephrotoxicity, thrombocytopenia etc. Amphotericin B-associated nephropathy is the major adverse effect and it involves both glomerular and tubular alterations (1, 2).

RESULTS AND DISCUSSION

Conventional AmB, Modifications of its Physical State and Lipid Formulations of AmB

Although AmB has been used in therapy more than 40 years, its physic-chemical properties, mechanism of action, and pharmacokinetics as well as pharmacodynamics have not been fully understood yet. Recently, important findings have been revealed in this area. Dimers stabilized by van der Waals interactions, linear or cylindrical aggregates of AmB were described in solutions or in artificial lipid membranes by spectroscopic measurements (3). In the absence of sterols, AmB aggregates remained at the surface of artificial lipid bilayers and induced only gel-to-subgel transformation of them whereas ergosterol present in membranes enables the embedding of AmB aggregates in phospholipid bilayers and consequently the formation of AmB pores (4). AmB caused an increase of the orientation order of lipid acyl chains in cholesterol-containing membranes but disorders of them in the presence of ergosterol (5). Based on molecular dynamics simulations, interactions between AmB and ergosterol are more specific and the channels are larger (and probably more stable) than those between AmB and cholesterol (6). However, the interactions of AmB with various sterols depend of the AmB/sterol molar ratio, and the greatest affinity has been found not to ergosterol but to 7-dehydrocholesterol (7).

AmB-related nephrotoxicity is dose-dependent and duration-dependent. Other risk factors are male sex, increased body weight, chronic renal disease, and exposure to other nephrotoxic drugs, e.g. cyclosporin (8). Infusion-related adverse effects of AmB are associated with the expression of several genes encoding pro-inflammatory cytokines and chemokines (9). Other toxic effects of AmB, such as hepatotoxicity (10) or pancreatic toxicity (11), have been observed relatively rarely. AmB exhibited a sporicidal activity in both in vitro and in vivo experiments (12).

In the last decade, three lipid formulations of AmB have been introduced into practice to improve its properties and to reduce its toxicity: AmB lipid complex (ABLC), AmB colloidal dispersion (ABCD), and liposomal AmB (L-AmB). The pharmacokinetics and tissue distribution of these formulations are different from those of conventional AmB, and from each other as well, whereas their efficacy and spectrum of activity are similar to conventional AmB. Lipid formulations significantly reduce risk of mortality and nephrotoxicity but the reduction of acute infusion-related reactions is not significant (13-15). Because of their high cost, lipid formulations of AmB are indicated after the failure of conventional AmB treatment or in the case of nephrotoxic reactions (15). A comparative analysis of ABLC, ABCD, and L-AmB was recently published (16).

Heating of AmB-deoxycholate to 70 °C for 20 min induces a superaggregation of AmB which is connected with a decrease of toxicity (probably by a lower induction of cytokine and chemokine production), whereas antifungal activity is similar and antileishmanial activity is higher in the comparison with conventional AmB (17, 18). In the connection with treatment of leishmaniasis, a nanosuspension of AmB has been developed which shows high adhesion to gastrointestinal mucosa and enables an uptake of AmB via the gastrointestinal tract (19). Although its antifungal activity has not been evaluated yet, this nanosuspension is an interesting example suggestive of possibility that an oral form of AmB for antifungal treatment could be developed. New amphiphilic copolymers for delivery of AmB also appear to be promising (20).

However, some other, relatively simple and inexpensive ways can contribute to a reduction of AmB toxicity: massive hydration and sodium supplementation (21), solubilization of AmB by cheaper synthetic bilayer fragments instead of treatment with AmB lipid formulations (22), or continual infusion of AmB-deoxycholate instead of traditional administration of the same dose during 4-6 h (23).

Conjugates of AmB with Polymers

lity, lower toxicity to mammalian cells and comparable in vitro antifungal effect with AmB against Candida albicans. However, the incorporation of MFAME into liposomes did not further improve its toxicity (30).

**CONCLUSION**

This review paper with 30 references includes new findings concerning amphotericin B, an important antifungal drug for the treatment of systemic fungal diseases. Several strategies have been used to increase the therapeutic index of AmB, e.g. modifications of AmB molecule or modification of its physical state (“heated” AmB), incorporation of AmB into lipid formulations, and conjugation of AmB with polymers.

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