

Therapeutic considerations to reduce adverse effects of amphotericin: chinese patient diagnosed with coccidiomycosis in Tijuana, Mexico

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ABSTRACT

Coccidioidomycosis is a mycotic disease endemic to Southern California, possibly extended to the border region of Tijuana in Baja California and other parts of northern Mexico ^{1,2,3}. There are several therapeutic alternatives for this disease. One of the most common drugs used for treatment is Amphotericin B (AMB), that despite its efficacy, side effects are occasionally so severe that in certain cases suspension of treatment is required ^{4,5}. Other drugs used currently are fluconazole, itraconazole, certain triazoles and echinocandins that can be prescribed as a monotherapy or combined, offering new treatment alternatives for chronic or disseminated Coccidioidomycosis, essentially establishing a therapeutic choice. We present the case of a 19-year-old male patient of Chinese origin, with an original diagnosis of Kaposi's sarcoma, whom after having skin biopsies it was determined that it was Coccidioidomycosis and the treatment was AMB and other drugs to which he presented adverse reactions. Alternatives were sought to reduce these adverse reactions, obtaining satisfactory results for the patient.

Keywords: Coccidioidomycosis, Amphotericin B, side effects.

Consideraciones terapéuticas para reducir los efectos adversos de la anfotericina: paciente chino diagnosticado con coccidiomicosis en Tijuana, México

RESUMEN

La coccidioidomicosis es una enfermedad micótica endémica del sur de California, posiblemente extendida a la región fronteriza de Tijuana, Baja California y norte de México ^{1,2,3}. El tratamiento empleado para esta enfermedad es diverso, entre los antimicóticos más utilizados está la Anfotericina B (AMB), a pesar de su efectividad, sus efectos adversos son tan severos que en algunas ocasiones han provocado la interrupción del tratamiento ^{4,5}. Actualmente se utiliza el fluconazol, itraconazol, algunos triazoles y equinocandinas como monoterapia o combinados, los cuales ofrecen una nueva alternativa en el tratamiento de la coccidioidomicosis crónica o diseminada. Presentamos el caso de un paciente masculino joven de 19 años de origen chino, diagnosticado inicialmente con sarcoma de Kaposi, posteriormente se practicó una biopsia de tejido donde se encontró coccidioidomicosis diseminada, la terapia fue AMB y diversos fármacos a los cuales presento reacciones adversas. Se buscaron alternativas para disminuir estas reacciones adversas, obteniendo resultados satisfactorios para el paciente.

Palabras claves: Coccidioidomicosis, anfotericina, reacciones adversas

INTRODUCTION

There have been reports of multiple side effects in therapy with Amphotericin B (AMB) such as fever, gastrointestinal problems, nausea, hypokalemia, metabolic acidosis, increase in serum creatinine levels, azotemia, nephrotoxicity, hepatic and neurologic effects and occasionally normochromic anemia, therefore, whenever administering this drug, levels in serum potassium should be regularly assessed, as well as renal function and febrile antigens and use of antipyretics and antihistamines if necessary. Drug delivery systems like liposomal formulations and lipid emulsions have been developed to diminish its side effects and improve absorption. While they allegedly have the advantage of being less toxic, their high cost limits their use in our setting. On the other hand, these products only improve its tolerance, since drug potency remains similar to the drug in its non-mixed form ^{4,5}.

CASE DESCRIPTION

We present the case of a 19-year-old Asian male, previously healthy in China with 4 years of residence in Tijuana, Mexico. He was admitted to our hospital after 30 days of showing increased signs of poor health, unchecked hyperthermia, weight loss, with no respiratory symptoms, occurrence of lesions on face (Fig 1) and upper extremities and one week before admission he complained of liquid stools and a depression of alertness, even after ambulatory polytherapy with antibiotics and little response.

While a diagnosis of Kaposi's sarcoma was made at admission, he initiated therapy with itraconazole (100 mg/day orally), ciprofloxacin (400 mg/day intravenous), amikacin (1 g/day intravenous), still presenting hyperthermia up to 40 °C and sleepiness. Cerebrospinal fluid showed increased levels of protein and polymorphonuclear leucocytes, and a skin biopsy showed coccidioidomycosis. Thera-

py was modified to Amphotericin B (50 mg intravenous/day) along with fluconazole (400 mg every 12 hrs orally). Following treatment, the patient displayed an increased level of alertness and improved general condition, although with persistent fever. Blood tests showed increased leukocyte count up to 30,000 with neutrophilia. Physical examination showed that the decreased volume of skin lesions is minimal, and no signs on a ganglionic or pulmonary level. After four weeks the accumulated dose of AMB was 1.2 grams, with elevated liver enzymes (AST= 200 IU/L, ALT= 130 IU/L, GGT =97 IU/L), persistent hyperthermia and a deteriorated condition, prompting to discontinue AMB therapy resulting in a slight improvement and significantly reducing hyperthermia. The regimen was changed to add voriconazole (200 mg/day orally) however the patient exhibits diplopia, dermal lesions, skin rash on neck and thorax, diaphoresis, tachycardia and convulsions so therapy continues only with fluconazole (400 mg/day orally)^{5,6,7}. After 12 weeks, *Pseudomona* sp was discovered in blood samples and the catheter's tip. Meropenem is added but the patient developed skin erythema, tachycardia, vomiting and hypertension⁸, and therapy is changed to ceftazidime (1 g intravenously every 8 hrs.). A control hemoculture is negative after two weeks of treatment. Neurologic evolution is characterized by a variation in his state of alertness with a tendency to drowsiness with periods of lucidity, intermittent fever and presence of submaxillary adenopathies. At the same time the patient also showed an increased swelling of the right knee. After 14 weeks of hospital care, decline in the patient's health was evident with persistent fever, disorientation, cephalgia, vomiting, and arterial hypertension and at that stage in his condition a new doctor is assigned to his care. The doctor assigned to the case, allowed for the hospital's clinical pharmacist to collaborate, who made an assessment of the patient's pharmacotherapy and arranged and documented all adverse reactions - voriconazole (diplopia, dermal lesions, skin rash on thorax and neck, diaphoresis, tachycardia, convulsions)^{5,6,7}, and meropenem (erythema, tachycardia, vomiting, hypertension)⁸, as well as the patient's susceptibility to experience these reactions. Trying to establish all parameters in this case, the treating physician orders blood samples to determine levels of CD4 (661 cel/uL) and CD8 (cel/uL), (CD4/CD8=0.85) and verify if his accelerated health decline was due to immunosuppression. After 15 weeks of hospital stay, the pharmacist proposes to reintroduce of therapy with AMB⁴ was not having

Fig 1. Ulcerating erythematous nodule on the face and histology shows granulomatous inflammation with presence of fungal microorganisms suggestive of coccidioidomycosis.

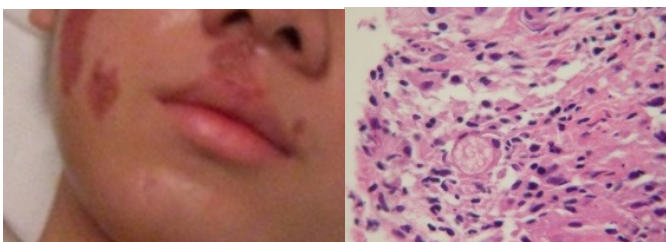


Fig 2. Therapeutic scheme helped to decrease the adverse reactions of AMB.

THERAPEUTIC CONSIDERATIONS

- Premedicated with 1 liter of Hartmann's solution, paracetamol (1 gram orally), diphenhydramine (4 mL intravenous), hydrocortisone (100 mg intravenous every 48 hours).
- Administration Amphotericin B, 40 mg, in 500 ml of saline solution for 4 hours every 48 hours.
- Itraconazole after meals (to increase its biodisponibility) 800 mg c/48 hours.
- Avoiding a combination of neurotoxic drugs.
- Frequent evaluation of renal and biliary function and electrolytes levels.

many other options at our disposal, but this time to avoid complications and adverse reactions, AMB therapy was done according to literature and medical studies based on evidence published by Dr. Laniado R. and col.⁴. This therapeutic scheme helped to decrease the adverse reactions of AMB, (Fig. 2).

After administering 480 mg of AMB no liver, renal or hematologic complications were shown. Furthermore, the patient had 800 mg of itraconazole every other day reacting satisfactorily. After 23 days of premedication and AMB treatment, the patient was released from the hospital in good condition, continuing with the same ambulatory treatment with Amphotericin for 10 more weeks up to an accumulated total of 1.2 grams.

DISCUSSION

Literature on cases of Chinese patients with coccidioidomycosis is very limited, because on the Asian continent is not considered to be an endemic zone and the reported cases are from California, Arizona and the North of Mexico. Patients with coccidioidomycosis have high mortality and morbidity. It's unknown if there is an immunological predisposition specific to these individuals, but what is known is that they are at a higher risk of contracting a serious coccidioidomycosis infection with lung and disseminated disease^{1,2,3}. In this particular situation it was apparent that there was little experience in refractory cases. There was a lack of an alternative treatment in addition to the complexity of ethnic variability there are some slow acetylators in the Chinese popula-

tion (acetylation speed is genetically controlled and slow acetylators are recessive autosomal inherited) which tend to accumulate the original medication in the body, thus increasing its toxicity. This was evident when our patient showed a serious adverse reaction to voriconazole which is metabolized through the liver cytochrome P450 isoenzymes CYP2C19, CYP2C9 and CYP3A4 and exhibits genetic polymorphism, individual or population variability (Asians), increased and extended plasmatic levels of slow metabolizers, a wide volume of distribution in tissue, 58% of plasma protein binding and nonlinear kinetics (reaching a steady state after 5 to 6 days of treatment), and to meropenem, a drug that distributes very well in tissue and biological fluids (well tolerated by the majority of patients)^{5,6,7,8,10}.

Due to drug pharmacokinetics, ethnic/population variability and the health deterioration of our patient, we recognized that he had a significantly larger propensity to exhibit pharmacological toxicity and required adjustments in some drug dosages^{9,10}. Complications were significant but with the alternative pre-medication treatment, we managed to lower adverse reactions to AMB and provided a suitable approach to therapy (considering pharmacokinetics and ethnic variability) such as prescribing itraconazole after meals to increase its biodisponibility, also aiming to build muscle mass and administering parenteral nutrition, helping our patient to withstand therapy with antifungal drugs that generally have a strong binding to plasma protein and tissue which the patient lacked. Thanks to this therapy the patient was able to recover. He was released from the hospital after 128 days. He completed his AMB therapy as an outpatient with good results.

We considered this to be an interesting case to be published due to the limited information available and the lack of data (prevalence) in dealing with this disease in our country³. Furthermore, there were no similar cases of Chinese patients in our country that had an effective alternative treatment. Also, thanks to published articles by other Mexican colleagues we were able to adapt therapy to our patient with our own resources with good results. Additionally, we would like to emphasize that this work was a team effort involving along with the physician, the hospital's clinical pharmacist (uncommon in our setting) and nursing personnel in assisting in our patient's recovery after a declining health and guarded prognosis.

Derived from the results of this treatment, the use of amphotericin and concomitant therapy in patients with mycotic diseases was standardized, allowing the reduction of adverse reactions such as renal damage and the optimization of therapy.

This case has been reported to the National Center for Pharmacovigilance.

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