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TOXIC EFFECTS OF HIGH DOSES OF AMPHOTERICIN B IN THE TREATMENT OF PARACOCCIDIOIDOMYCOSIS

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SUMMARY

The delayed toxic effects of high doses of amphotericin B in two patients of paracoccidioidomycosis are reported. The patients received during a period of 4 to 8 years total doses of 30.5 and 26.0 gm of amphotericin B in many series of injections following relapses of the disease. The toxic effects on the kidney, liver, hematopoietic system and adrenal glands are analised. Azotemia, alterations in the creatinine clearance and hypokalemia were due to irrerversible chronic toxic nephritis confirmed by histopathological and electron microscopic studies. The immunofluorescent test did not show any immunocomplex in the renal tissues which excludes the possibility of an immunological alteration. The abnormalities of the ventricular repolarization in the electrocardiogram were attributed to hypokalemia. Anemia was related to azotemia. It was not observed any toxic effect of the amphotericin B in the liver, nervous system and adrenal glands.

INTRODUCTION

Amphotericin B introduced in the treatment of paracoccidioidomycosis in 1958 [17] has been the elective therapy of the disease whose prognosis improved with its use [14,15,20,21,23,24]. The usage of amphotericin B produces immediate side effects (fever, chills, nausea, vomiting) which are controlled with the technique in administering it and delayed side effects. The delayed side effects like anemia, hypokalemia, enhanced urea and renal alterations [14,23,24], electrocardiographical and cardiac area alterations [12,23] can be severe. The nephrotoxicity of amphotericin B was studied by several Authors [2,6,7,8,25] and the alterations were described at the optical and electronic microscopy in the glomeruli and renal tubuli [10,11]. The studies regarding the nephrotoxicity of amphotericin B were generally done in patients in whom the total doses administered were around 2.0 to 5.0 gm being usually reversible. By increasing the dose an irreversible renal lesion may occur [7,27]. Irreversible renal lesions causing deaths occurred in two patients of ours after total doses of 10225 mg and 8675 mg but another patients have tolerate higher total doses, which suggests an individual component in the nephrotoxic action of the drug [14]. On administering amphotericin B electrocardiographic and cardiac area alterations occur but irreversible delayed cardiac alterations are not described. On the other hand delayed hematological, nervous system and adrenal glands alterations have not been described but a portal fibrosis was reported in the liver [4].

In this paper we study the delayed toxic effects of amphotericin B in two patients of paracoccidioidomycosis who received a very high total doses of 30.5 gm and 26.0 gm of amphotericin B during 4 and 8 years, respectively.

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CASE REPORTS

Case 1 — Male, white, 28 years of age with a cutaneous-lymphatic form of paracoccidioidomycosis received several series of amphotericin B from 1973 to 1977 with the total dose reaching 30.5 gm. He also received in the mean time sulfadimethoxine. Amphotericin B was dissolved in 500 ml of a 5% dextrose solution administered by slow intravenous drip over a period of 6 hours. In order to prevent the immediate side effects it was added 25-50 mg of hydrocortisone sodium succinate or similar corticosteroid to the dextrose solution. According the degree of the immediate side effects the dose of corticosteroid was lowered. In a series the patient received initially amphotericin B daily and later in alternate days. After the first two infusions of amphotericin B the patient received 100 mg of amphotericin B given daily until clinical and mycological cure. The patient had many relapses in spite of having taken 2.0 gm a day of sulfadimethoxine in the intervals of the series of amphotericin B. The relapses of the diseases were established by clinical mycological, and histopathological examinations and the titers of serological reactions (Fava Netto's tests). The examination of the patient 7 months after the last treatment of amphotericin B showed the following results: hypoproteinemia and hypopotassemia (3.2 m Eq/1), increase of creatinine (3.7 mg/100 ml), urea (77.0 mg/100 ml), proteinuria (0.1 g/1) and low clearance of endogenous creatinine (27.0 ml/min). The tests for hepatic and adrenal functions were normals. The cardiac area was not altered and the electroencephalogram did not show alterations. The electrocardiogram showed decrease of the T wave and slight increase of the U wave. The renal biopsy showed focal tubular atrophy with thick collagen bundles and arterioles with swelling of the endothelial cells. Glomerules were not observed. The direct immunofluorescent test with difference conjugates (anti-IgG, anti-IgM, anti-IgE, anti-IgA and anti-complement) did not show any deposit of immunoglobulins. The electron microscopy glomerular alterations were more evident at the level of the tubules, with the brushlike edge in the proximal tubules disappearing, and loss of the cellular connection. It was seen also a vacuolization and rarefaction of cytoplasm with increase of the dense bodies; diffuse vacuolization of the muscular cells of the small arteries, enlargement of the cisterns and degenerative changes in the lining cells. Nuclear alterations were not observed.

The liver biopsy did not show any alterations in the optic and electron microscopy.

Case 2 — Male, white, 26 years of age, had a muco-cutaneous and lymphatic form of paracoccidioidomycosis since 1969 and he was treated for 8 years with series of amphotericin B, the total dose reaching 26.0 gm.

Amphotericin B was given in similar manner than that of case 1, but the standard dose was 75 mg daily (1.1 mg/kg/weight). Patient also received for different periods of time sulfadimethoxine (2.0 gm/day). The clinical examination and tests 6 months after the last series showed hypokalemia (3.4 mEq/1) and slight increase of urea (47.0 mg/100 ml). The clearance of endogenous creatinine was greatly impaired (5.5 ml/min). There was hypoproteinemia by decrease of albumin and alpha-1. Tests of liver functions showed evident alterations; transaminases were increased (TGO: 43u. and TGP 53u.) and BSP depuration was altered (retention of 16.5%). The plasmatic cortisol showed a slightly decreased in the adrenocortical reserve. The assessment of the cardiological area and the electroencephalogram did not show any alterations. The electrocardiogram showed a similar pattern to that of Case 1.

The renal biopsy showed partial and total hyalinized glomerules with fibrosis of the Bowman's capsule. In certain areas the tubules were preserved and in others atrophic zones with interstitial fibrosis, were seen with mild inflammatory lymphocytic infiltrate and hyaline thickening of the basal tubular membrane. In conclusion there were tubular atrophy with glomerular hyalinization (Figs. 1-2). The direct immunoglobulin tests were negatives and in the electron microscopy the alterations were similar to those reported in the Case 1.

The liver biopsy showed histopathological and electron microscopy alterations probably related to a previous hepatitis confirmed by the positive test with Au antigen, in the serum.

COMMENTS

The observations of two patients who received high doses of amphotericin B, unique in literature, permited to evaluate the delayed

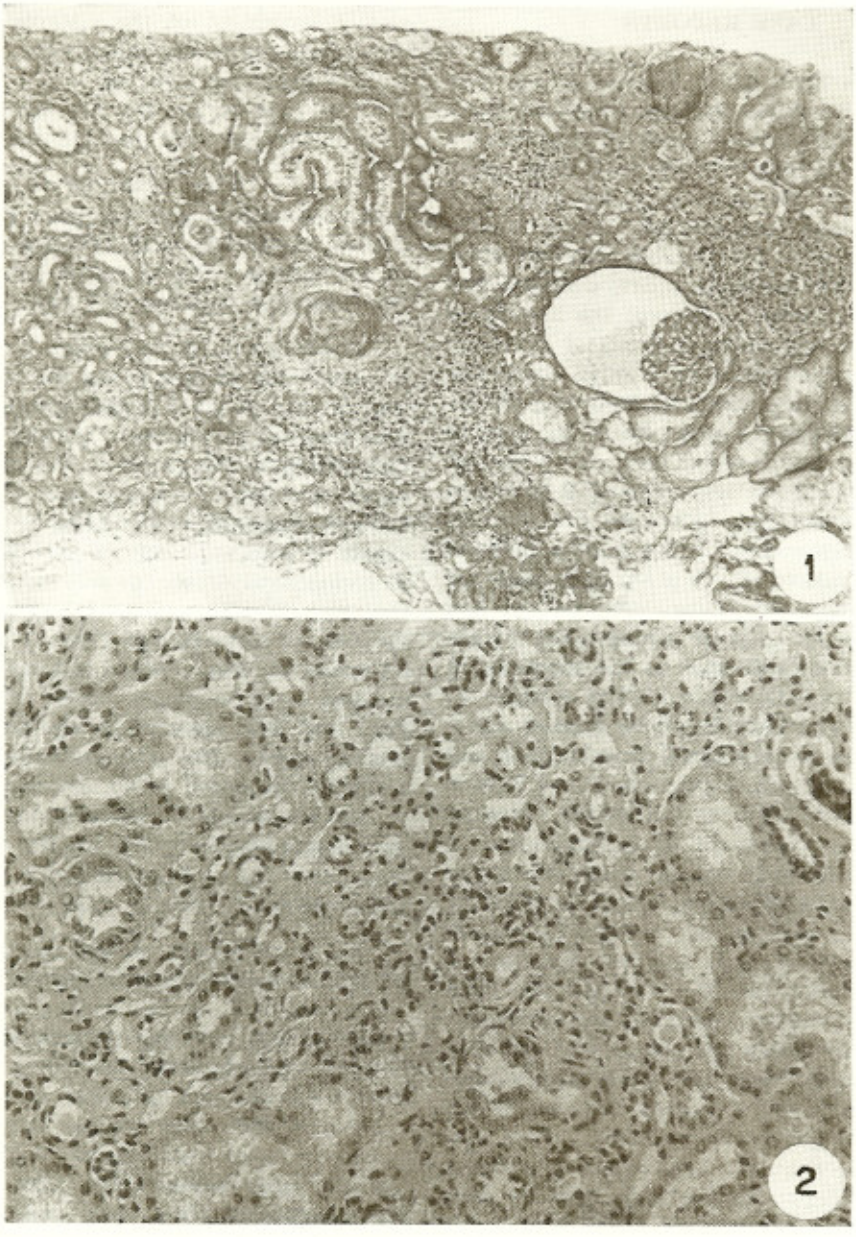

Fig. 1 — Case 2 — Kidney: atrophic and hyalinized glomeruli. Tubular atrophy, interstitial fibrosis and inflammatory lymphocitic infiltrate. H.E., 160 ×

Fig. 2 — Case 2 — Kidney: Detail of the interstitial fibrosis and tubular atrophy, with a lymphocitic inflammatory infiltrate in the central area. H.E., 400 ×

side-effects of the treatment. The most important side-effects were the nephrotoxicity of the amphotericin B. Azotemia was increased in both patients. Case 1 who took a larger dose of the drug during a shorter period of time than Case 2 had a higher azotemia, which confirmed previous reports [7,22,23]. Clearance of endogenous creatinine was highly impaired in both patients and the serum creatinine was increased in Case 1. These alterations can also be related to the doses of amphotericin B. The urinalysis [1] carried out during the treatments did not show any significant abnormality. Anemia can be observed during the treatment and it was seen

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in both cases. The anemia was related to the toxic effect upon the bone marrow [3,23] or due the hemolysis [16] or it is related with azotemia [19]. In Case 1 high azotemia and severe anemia were observed. The hypokalemia referred by many Authors [5,10,16,19,23] was attributed to the alterations of the tubular functions [5,19]. The renal alterations with the increased dosage by the series of treatments can become irreversible. The electrocardiographic alterations in T and U waves described since 1960 [26] are attributed to kypokalemia [9,18,26]. The corticosteroid given together with amphotericin B would diminish the cardiac toxicity but would not modify the intracellular hyperkalemic effect. The alterations of the cardiac area which were noticed [12,23] were reversible and were not found in these cases. Hypofunction of the adrenal glands are reported in paracoccidioidomycosis [13] due to the localization of the disease in the glands. Amphotericin B probably has not toxicity upon the adrenals as seen in Case 1 with normal adrenal response in spite of the high doses of amphotericin B. The slight decrease in the adrenal response in Case 2 may be due to the adrenal localization of the disease. The results of clinical and neurological examinations and electroencephalogram did not show any toxic effects of amphotericin B.

The histopathological findings in the renal biopsies showed chronic alterations characterized by glomerular hyalinization, tubular and interstitial fibrosis, tubular degeneration and swelling of the endotelial cells of the capillaries with a lymphocitic infiltrate. According the classification of renal lesions [10] these alterations can be included in group III. The direct immunofluorescent tests were negative in both cases showing that the alterations were due to the toxic effects of the drug without immunocomplex. The electron microscopy showed the alterations which have been previously described [11]. The liver functions were normal in Case 1 in spite of high doses of amphotericin B and they were impaired in Case 2 who developed hepatitis during the treatment. The electrophoresis and the immunoelectrophoresis did not show any alterations.

In conclusion the study of two patients treated with high doses of amphotericin B showed that the main delayed toxic effect of the drug is the nephrotoxicity, which according to the dosage can be irreversible.

RESUMO

Efeitos tóxicos de altas doses de anfotericina B no tratamento da paracoccidioidomicose

Os efeitos tóxicos tardios das doses altas de anfotericina B em dois doentes de paracoccidioidomicose são relatados. Os doentes recebiam em períodos de 4 e 8 anos doses totais de 30,5 g e 26,0 g de anfotericina B em series sucessivas para tratamento de recidivas. Os efeitos tóxicos tardios da droga são estudados. A uremia, alterações da creatinina e a hipopotassemia encontradas decorrem da nefrite crônica tóxica irreversível confirmada pela biopsia renal em microscopia óptica e eletrônica. Os estudos com imunofluorescência não revelaram imunocomplexos nos tecidos renais o que exclui uma alteração imunológica. As alterações de repolarização ventricular do eletrocardiograma são causadas pela hipopotassemia. A anemia é decorrente da uremia. Não foram encontrados efeitos tóxicos da anfotericina B no fígado, sistema nervoso e suprarrenais.

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