Rhabdomyolysis associated with pentamidine isethionate therapy for American cutaneous leishmaniasis

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Sir,

In the case of American cutaneous leishmaniasis, the risk of serious morbidity from cutaneous and mucocutaneous forms requires highly effective parenteral therapy. Pentavalent antimony compounds have been the mainstay of antileishmanial therapy for half a century. However, despite high effectiveness, these drugs require long duration regimens and cause frequent and serious toxic effects. Short courses of pentamidine isethionate therapy have been shown to be highly effective and acceptably tolerated as an alternative to antimony in the treatment of Viannia subgenus American cutaneous leishmaniasis.1

In French Guiana, where Leishmania [V] guyanensis is predominant, pentamidine mesylate was first used with different regimens from 1980 to 1992 at Cayenne hospital. Since 1992, short courses of pentamidine isethionate have been used successfully as a first-line therapy for cutaneous leishmaniasis. Since late 2000, the effectiveness and safety of an intramuscularly administered single-dose therapy of 7 mg/kg of pentamidine isethionate have been evaluated as a standard outpatient treatment for cutaneous leishmaniasis at Cayenne hospital. Rhabdomyolysis appears to be an extremely frequent adverse effect of pentamidine isethionate.

A total of 45 patients with cutaneous leishmaniasis were seen between November 2001 and May 2002 at Cayenne hospital. They received a single intramuscular dose of 7 mg/kg of pentamidine isethionate (Pentacarinat; Aventis). Venous creatine kinase (CK) level was assessed at days 2 and 15 after the injection. At 2 months follow-up, patients were asked what adverse effects of treatment there had been.

Early CK levels were measured for 26 out of 45 patients, showing substantially increased CK levels (>1000 U/L) in 19 (73%) patients (range 1032–9312 U/L, median 3096 U/L). Early CK levels were normal (<165 U/L) in three (11.5%) patients, and slightly increased (>165 and <1000 U/L) in four (15.5%) patients. When assessed in the high CK level cases, urea and creatinine levels did not reveal any renal failure related to rhabdomyolysis. Potassium and calcium levels were within normal limits as well. Late CK levels were measured for 18 out of 45 patients, and CK levels had normalized in 12 patients and were close to the normal range in the other six. At 2 months follow-up, 27 out of 45 patients were seen, including 16 of the 23 patients with increased early CK levels. All patients were asymptomatic. Frequent transitory local pain at the injection site was reported. No other complications had occurred for the patients with pentamidine-induced rhabdomyolysis at this 2 month follow-up.

Most of the adverse effects of pentamidine are well known, and are usually mild to moderate when using short-course, intramuscular regimens.2,3 Pain at the injection site is the most frequent adverse effect, whereas acute hypotension, nausea, vomiting and hypoglycaemia are less frequently reported. Severe pentamidine adverse effects, such as diabetes mellitus and nephrotoxicity, have been associated with high cumulative doses of pentamidine. Indeed, most cases have been reported in the setting of visceral leishmaniasis and AIDS-related Pneumocystis carinii pneumonia, for which a prolonged treatment is required.

Rhabdomyolysis is not recognized as a toxic adverse effect of pentamidine either by drug manufacturers or in reviews of pentamidine. Only a few cases have previously been reported in the literature. Sensakovic et al.4 first reported a case of pentamidine-induced rhabdomyolysis with acute renal failure in a human immunodeficiency virus (HIV)-infected man treated for P. carinii pneumonia with pentamidine (4 mg/kg/day, intramuscularly, for 7 days). The outcome was fatal after peritoneal dialysis. Lighthurn et al.5 noted an increased CK level in all of 37 patients treated for American cutaneous leishmaniasis with pentamidine isethionate (two intramuscular injections of 7 mg/kg, with an interval of 48 h). No complications were reported. Finally, Lieber-Mbomeyo et al.5 recently reported two cases of rhabdomyolysis after pentamidine isethionate therapy for American cutaneous leishmaniasis (two intramuscular injections of 7 mg/kg, with an interval of 48 h). No complications were reported.

It is known that even a single intramuscular injection of various drugs can induce mild CK elevation of usually 2–6×
normal. Non-specific CK elevation related to the use of the intramuscular route of administration appears to correlate with the osmolarity of the solution and the volume of the injectate. Indeed, Sidell et al.\textsuperscript{6} showed that intramuscular injection of isotonic sodium chloride alone or injection of low concentrations of a drug (pralidoxime chloride) induce only negligible elevations in CK activity, whereas CK increase of two to three times normal is seen when using the drug or sodium chloride at an osmolar concentration of >1500 mOsm/L. In our study, we found significant CK elevations of 6–50× normal, although the commercial preparation of pentamidine isethionate (30 mg/mL) has a low osmolarity of 151.8 mOsm/L, and when the volume of the injectate was >10 mL, half of the volume was administered in each buttock. Thus, the CK elevations we observed are likely to be related to a specific toxicity of pentamidine isethionate on muscle tissue rather than to a non-specific result of the use of the intramuscular route of administration. We use pentamidine isethionate at a higher dose (7 mg/kg) than the standard 4 mg/kg, on the basis of our experience of decreased effectiveness after switching from pentamidine mesylate to pentamidine isethionate, 4 mg/kg, in 1992. Indeed, 4 mg/kg of pentamidine mesylate contains 4 mg/kg of pentamidine base, whereas 4 mg/kg of pentamidine isethionate contains only 2.3 mg/kg of pentamidine base. We found that a 7 mg/kg dose of pentamidine isethionate, i.e. 4 mg/kg of pentamidine base, restores effectiveness similarly to a 4 mg/kg dose of pentamidine mesylate. Pentamidine toxicity has mainly been associated with high cumulative doses; however, we cannot exclude the possibility that the incidence of adverse effects might be increased by using a higher daily dose of pentamidine isethionate than the standard dose of 4 mg/kg.

Even if no complications related to rhabdomyolysis had occurred in our study, we recommend pentamidine-induced rhabdomyolysis to be carefully monitored when using this treatment, as it might account for an underestimated part of pentamidine nephrotoxicity.

References