Systemic Meglumine Antimoniate in Cutaneous Leishmaniasis of Children: Clinical and Laboratory Complications

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Children account for 7%–20% of cutaneous leishmaniasis cases in Iran, but there are few safety data to guide pediatric antiparasitic therapy. We evaluated the clinical and laboratory tolerance of the systemic pentavalent antimonial compound meglumine antimoniate, in 70 Iranian children with cutaneous leishmaniasis. Adverse effects were similar to those seen in adults.

Key words. adverse effects; children; cutaneous leishmaniasis; meglumine antimoniate.

Cutaneous leishmaniasis (CL) is one of the most common endemic diseases in the Khorasan province of Iran, including the city of Mashhad. Cutaneous leishmaniasis in Mashhad is mainly due to Leishmania tropica [1].

Cutaneous leishmaniasis can occur at any age and often causes cosmetic disfigurement, and the infection can lead to significant morbidity as well as social stigma [2]. The frequency of childhood CL is relatively high, especially during the second decade of life. Children are among the highest risk groups for CL, and in some reports CL accounts for 7%–20% of all patients referred to clinics [1, 3].

A simple, more convenient therapy with high efficacy and few side effects has long been sought [4]. In spite of the different treatment modalities that have been proposed (topical, intralesional, or systemic antiparasitic therapy), systemic pentavalent antimonials are still the treatment of choice. In the United States, sodium stibogluconate is used; however, in much of the rest of the world, meglumine antimoniate is the treatment of choice, particularly for adults. Children have a lower response rate to antimonial drugs, and they have a higher elimination rate of antimony than do adults [4–6]. Thus, it has been proposed that, based on weight, children require higher doses of the drug than adults; however, not enough data exist to indicate whether children will suffer more adverse effects with such therapy [5–7].

Therefore, we evaluated the clinical and laboratory adverse effects of systemic meglumine antimoniate in outpatient children presenting for treatment of CL.

MATERIALS AND METHODS

In a prospective case series study, 89 children under the age of 13 who were referred to the leishmaniasis clinics of Qaem and Imam Reza hospitals (Mashhad, Iran) between March 2010 and April 2011 were enrolled. The diagnosis was parasitologically confirmed by using Geimsa-stained direct smear. Cases with definite indication for receiving systemic meglumine antimoniate therapy were selected. The following children were excluded from the study: those receiving another type of medication for this disease; with a medical history of hepatic, renal, cardiac, or hematologic disease; recent pancreatitis; or with baseline values of hemoglobin, amylase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and serum urea nitrogen outside the normal range.

A full medical history was taken and a thorough physical examination was performed to rule out other underlying diseases. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from each child’s parent or guardian before the child was enrolled.

Each patient was administered intramuscular injections of meglumine antimoniate (Glucantime; Sanofi Aventis, Paris, France) at a dosage of 20 mg of pentavalent antimony/kg per day for 20 days. The patients were strongly advised not to use any other therapeutic method during this period. Laboratory tests, including complete...
blood counts, liver and kidney function tests, serum amylase, and lipase, were performed to monitor potential drug-related toxicity at the following time points: (1) before initiating treatment, (2) in the middle of the treatment course, and (3) finally at the end of the treatment course on day 20. Children presenting with abnormal laboratory values were monitored until their values normalized.

Clinical adverse events such as myalgia, pain, erythema, etc were identified and recorded in a designed questionnaire during treatment and in each follow-up visit. The χ² test, paired sample t test, and the Wilcoxon test were used as appropriate to determine statistical significance (P < .05), using SPSS software (version 13; IBM Company, United States).

RESULTS

In this study, 89 children with CL were enrolled initially. Of these patients, 19 were excluded for the following reasons: they were taking another treatment, they did not complete the treatment course, or they were lost to further follow up. In total, 70 patients completed the study. Sixty patients (85.7%) received a single 20-day treatment course, whereas 2 treatment courses were administered for the other 10 (14.3%) patients. Table 1 shows the demographic characteristics of the 70 children who completed the study.

Among the 70 patients who completed the study, 14 experienced clinical adverse effects of systemic meglumine antimoniate therapy: erythema of the injection site (18.6%) and protracted pain (10%) were the most common side effects. A few patients also experienced inflammation, myalgia, anorexia, and fever; 31 (44.3%) patients experienced no adverse effects. Univariate analysis (χ² test) was performed, and no significant relationship was found between clinical adverse effects and either age or gender. No significant changes were observed in mean white blood cell counts, platelet counts, hemoglobin, or serum blood urea nitrogen (BUN), creatinine, or bilirubin levels before and after therapy (P > .05, paired t test). There were statistically significant elevations in serum concentrations of AST (serum glutamic-oxaloacetic transaminase), ALT (serum glutamic-pyruvic transaminase), amylase, and lipase, but these were clinically irrelevant (mean changes of <10 IU/L for hepatic transaminases and <30 IU/L for pancreatic enzymes). After all patients received treatment with meglumine antimoniate according to their age group, laboratory tests revealed no significant correlation (P > .05). No significant associations were seen between age and the laboratory values after therapy, or with age and the number of treatment courses of systemic meglumine antimoniate.

DISCUSSION

Leishmaniasis is a widespread parasitic disease considered to be endemic in 88 countries in both the Old and New World [6, 8]. Children have only recently been included in clinical trials, revealing a significantly lower response rate and significantly higher elimination rate of antimony compared to adults [5, 7, 9]. In most of the previous studies, side effects of meglumine antimoniate have been reported in a general population including both adults and relatively few children. Masmoudi et al [10] reported 87 patients aged 8–84 years who receiving systemic meglumine antimoniate. Arthralgia and myalgia were seen in 4 patients, fever was noted in 3 patients, nausea and vomiting were seen in 2 patients, and injection site erythema was observed in 1 patient, for an adverse event rate of 21%. In a prospective, randomized trial that compared the efficacy and side effects of miltefosine with meglumine antimoniate for CL in children, fever, loss of appetite, and mildly elevated transaminases were the most frequent clinical side effects in children who received meglumine antimoniate [5]. In these studies, the overall tolerance of systemic meglumine antimoniate in adults and children was similar to that of children in the present study.

In our study, the concentrations of direct and total bilirubin, creatinine, BUN, and hematologic parameters demonstrated no meaningful difference after treatment. The mean serum concentrations of lipase, amylase, ALT, and AST did increase during treatment but not to clinically important levels, and no clinical signs of pancreatitis or hepatitis were diagnosed in any of the patients studied. These findings are similar to those of Shahian et al [11], who investigated the effect of 20 mg/kg per day meglumine antimoniate on the pancreas during treatment of visceral leishmaniasis in 20 children. They concluded that (1) neither acute pancreatitis nor hyperamylasemia occurred

| Table 1. The Demographic Characteristics of the Patients Who Completed the Study |
|---------------------------------|-----------------|-----------------|
| Sex                             | No. (%)         |                  |
| Boy                             | 31 (44.3%)      |                  |
| Girl                            | 39 (55.7%)      |                  |
| Age (years)                     |                  |                  |
| Mean                            | 5.39 ± 3.11     |                  |
| Range (years)                   |                  |                  |
| <5 years                        | 31 (44.3%)      |                  |
| 5–10 years                      | 32 (45.7%)      |                  |
| 10–13 years                     | 7 (10%)         |                  |
| Mean weight (kg), (range)       | 18 (10–32.8)    |                  |
| Type of Lesions                 |                  |                  |
| Ulcer                           | 3 (2%)          |                  |
| Papule and plaque               | 131 (89.7%)     |                  |
| Nodule                          | 14 (8.3%)       |                  |
among immunocompetent children with visceral disease and (2) routine monitoring for serum amylase and lipase levels was not necessary [11].

Taken together, our data and those reported in older children and adults indicate that the adverse event rate of systemic meglumine antimoniate in children is similar to that of adults, and, in general, the drug is reasonably well tolerated. Nevertheless, continued monitoring of renal, hepatic, and pancreatic function during and immediately after antimonial treatment is prudent [12]. Some experts also perform electrocardiograms, although we were not able to routinely do so in this study [12].

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