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Short Communication

Therapeutic Options for Visceral Leishmaniasis in Children

Sujit K. Bhattacharya[1]*, Das Gupta RK[2], Mihir Bhattacharya[3] and Ganguly NK[4]

[1]*National Institute of Cholera and Enteric Diseases, India*
[2]*Former Joint Director, National Vector Borne Disease Control Programme, India*
[3]*National Institute of Cholera and Enteric Diseases, India*
[4]*Former Director General, Indian Council of Medical Research, India*

***Corresponding author**
Sujit K Bhattacharya, National Institute of Cholera and Enteric Diseases, Kolkata, India, Tel: 91 8697462003; Email: sujitkbhattacharya@yahoo.com

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Abstract

Children are a special group so far as drug treatment is concerned. The adult drug doses need to be carefully scaled down to suit the drug is available in a concentration which is safe and effective. Side effects in children may be different from that of in adults. In view of this, drug treatment in children requires careful dose calculation which is per kg body weight and not fixed doses. The calculation may be difficult in tablet or capsule form of the drug and may be done accurately when the drug is dispensed in liquid, syrup and suspension forms.

INTRODUCTION

This is particularly true when we consider drug treatment for children with Visceral Leishmaniasis (VL) [1] VL is a disease complex manifesting with prolonged fever (>14 days), anorexia, loss of weight, anemia and most importantly splenomegaly. A child presenting with long continued fever, malaria excluded, in an area endemic for VL, should be suspected to be suffering from VL and screened. Weight loss is particularly more conspicuous in children than in adults. Hair changes are more frequently seen in children.

Several decades back, dearth of safe and effective drugs poised a tremendous therapeutic challenge. Side-effects like pain at the site of injections with Sodium Stibogluconate [2] were troublesome and compromised with compliance. This drug is the oldest drug that has been in use over a century. It is effective against VL except in areas where drug resistance has developed. It is administered by intramuscular and intravenous routes. Drug resistance is a problem. In North Bihar in India, the parasites are resistant to antimonials. To overcome resistance, the dose and duration were increased, but toxicity was also increased proportionately. The serious toxicity of the drug is cadiotoxicity which may be fatal. The drug is given in a dose of 20-30mg/kg/day. Antimonials are relatively cheap and easily available. They are the first-line drug where resistance to the drug is minimal.

Now-a-days research demands multi-institutional Collaboration. In the field of new drug development for VL, collaborative efforts between several national and international institutions are golden example. When India, Nepal and Bangladesh, launched Kala-azar Elimination [3] from the three countries, common protocols were developed and used. Cross-border collaboration was strengthened. International Institutes like TDR (Tropical Diseases Research), University of Antwerp, Belgium, World Health Organization and UNICEF, assisted the programme for training and research. These collaborations resulted in developmemt of at least three drugs, namely, Miltefosine [4], Paromomycin [5] and Lipid Amphotericin B [6].

Miltefosine is the first ever oral drug developed as an intense collaborative effort of Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Balaji Uthan Sansthan and Kala-azar Research Centre from Indian side and Zanteris, Germany for Miltefosine and One World Health for Paromomycin. WHO/TDR provided training and research support. Phase I to III trials were conducted in Bihar, India. Children trial was also done in North Bihar in three Institutions. The efficacy of the drug was >95% and was relatively safe [7,8]. As a safety procedure child who were dehydrated were initially hydrated by ORS/ I.V fluids and the patient was build up by transfusion in children with severe anemia. Since infestations with worms were common, deworming was carried out before initiating trial drugs. Children were more compliant when these measures were taken before the trial started and minimized side effects. Miltefosine is contraindicated in pregnancy [9] and women of child-bearing age unless they use suitable contraceptive.

Paromomycin, an aminoglycoside, is the product of collaboration of Indian National Agencies and International Agency, OneWorld Health in a drug development mode in Bihar, India [10]. The efficacy of Paromomycin is >96% and safety is acceptable. Ototoxicity was not an absolute contraindication. It was safe in pregnancy [11]. Because of teratogenicity of Miltefosine in female and safety of Paromomycin it was suggested that Miltefosine should be used in children and adults with VL and Paromomycin for VL of females. This proposition did not find a place in the elimination Programme

Lipid Amphotericin B is considered as the first line drug for the treatment of VL both in children and adults in the Kala-azar Elimination Programme in the Indian Sub-continent [12].

From 2015 as per Kala -azar drug policy (www.nvbdcp.org) Lipid Amphotericin B is a first line of treatment for all VL cases in adult and children and Miltefosine for PKDL probable cases. NVBDCP has also approved Miltefosine + Paromomycin injection combination (10 days). However, indigenous manufacturers are not having license to produce and sell in India. Program is trying hard to get license for indigenous manufacturers through Drug Controller General of India (DCGI). States have also stopped for asking Amphotericin B deoxycholate from NVBDCP due to long duration treatment and its feasibility to use in field condition when a single day single dose (LAMB) is available. WHO is supplying Lipid Amphotericin B free to India. Ice Lined Refrigerators (ILRs) provided to facility centers for maintaining cold chain. In areas where power cut is prevalent, support of a generator is absolutely necessary. This drug is the safest of all anti-leishmanials. The drug is given in a single dose of 10mg/kg by the intravenous route in children as well as adults. Initial studies showed that it can also be given in dose of 3 mg X 5 days/day or 5 mg/kg for 3 days [13]. Universal safety procedure is required, while giving infusion, for prevention of HIV, MP, HBV and HCV. This drug is considered the best and safe drug for the treatment of VL. It is safe in children and is used in children who can afford it. Lipid Amphotericin B [6] is much safer than Amphotericin B. When resistance to Stibogluconate was mounting up, Amphotericin B [7] became the drug of choice. Side-effects include ototoxicity and nephrotoxicity. Another safe and effective drug was Urea stibamine which was lost as the developer of the drug unfortunately did not leave the composition before his death. Sitamaquine is undergoing development. Initial results are encouraging.

Essentially, Kala-azar is a neglected tropical disease. The disease is localized and epidemiology is unique. Children constitute a considerable portion of the total cases. In the Kala-azar elimination programme, adults as well as children were targeted for diagnosis and treatment. WHO Leishmaniasis country profile 2015 reported 31 % children <14 years were positive for visceral leishmaniasis through rK39 test . Miltefosine is an oral drug and Lipid Amphotericin B is the safest drug for VL. Both drugs are costly. In view of this, it is essential that new safe and oral drugs are developed and, in this effort, national and international agencies may forge collaboration for this noble effort. It is indeed necessary to mobilize funds for this effort.

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