Nigerian Journal of Paediatrics 1983; **10 (1)**: 19–22

Clinical Trial of Isoprinosine in Measles

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Summary

Onuora CU, Abdurrahman MB, Bala AS, Jibril HB and Effiong RI. Clinical Trial of Isoprinosine in Measles. *Nigerian Journal of Paediatrics* **1983; 10:19.** A placebo-controlled double-blind clinical trial of isoprinosine was carried out in 100 children with acute measles. The criteria used for assessing patients' response to treatment were clinical course of the disease and the rate of fall in temperature. When clinical course was used as the criterion, 85% of the patients on isoprinosine and 70% of patients on placebo responded well to treatment; the difference is not statistically significant. The temperature response of patients treated with isoprinosine was not significantly different from the response of patients who received placebo. However, all the four deaths occurred in the placebo group.

Introduction

MEASLES in African children is characterised by its occurrence in younger age groups, its severity, a high incidence of complications and a high mortality.[1-4] Although an effective measles vaccine has been available for some time, measles is still prevalent in many African countries. This is due to a combination of low immunization rate and the use of vaccine of uncertain potency. There is still, therefore, a need for an effective therapeutic agent against measles.

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Isoprinosine is a complex made up of inosine and a salt, dimethylaminoisopropanol-acetamidobenzoate, in a 1:3 molar ratio. It has antiviral activity[5,6] and immunomodulatory properties.[7-9] The drug has been shown to have antiviral activity against rhinovirus,[10] influenza,[11] herpes simplex[12] and hepatitis A.[13] Of particular interest are reports of some degree of success when isoprinosine was used in patients with subacute sclerosing panencephalitis, [14-16] a disease closely associated with measles virus. The drug has also been found to be effective in some cases of measles. [17,18] In addition to its antiviral action, isoprinosine might also be expected to be effective in measles by its immunopotentiation action, since measles is known to depress the patient's immunity. [19]

We report here, the results of a double-blind clinical trial of isoprinosine in the treatment of 100 children with acute measles.

Materials and Methods

The subjects were children with acute measles in the eruption phase, admitted to the Emergency Paediatric Unit, Ahmadu Bello University (ABU) Hospital, Zaria, from October 1981 to January 1982. All patients received symptomatic treatment with aspirin and topical eye antibiotic. Additional treatment such as systemic antibiotic was given as indicated. On admission, patients were classified as mild, moderate, and severe, using the criteria of Scheifele and Forbes.[20] A series of bottles numbered 1 to 100 and containing 20 tablets, each of 500mg, were supplied to the investigators who did not know which of these bottles contained isoprinosine or placebo. The first patient was treated with contents of bottle number 1 and subsequent patients were treated with the contents of bottles 2 to 100 serially. Any unused tablets were discarded. The dosage used was 50mg/kg body weight/24 hours divided into three doses, for five days. Decoding of the drug was done at the end of the trial, by an independent observer.

Assessment of response to therapy

(*a*) *Clinical course*

Very good. Accelerated recovery: improvement in clinical signs within three days of admission.

Good. Normal recovery: improvement within four to six days.

Fair. Protracted course: after initial improvement, there was worsening of patient's condition or development of complications.

Poor. No improvement or worsening and/or development of complications.

Bad. Rapid downhill course. Death.

(*b*) *Temperature course.* The time taken for admission temperature to drop from 38°C to 37°C.

Very good. Fall in temperature between first and second day of admission.

Good. Fall between 3-4 days.

Fair. Fall between 5-6 days.

Poor. Fall after 6 days.

Observations

Each patient was examined at least daily. The duration of admission for the trial was seven days but patients stayed longer if they were not considered fit for discharge. The following observations were recorded: general condition, temperature, diarrhoea, vomiting, development of complications and weight on admission and at discharge.

Investigations

The following investigations were carried out on admission and, as much as possible, at the time of discharge: haemogram (Hb, WBC), blood film for malaria parasite, platelet count, serum urea, electrolytes, amylase, lipase and proteins. Standard laboratory methods were used for these tests. The purpose of doing these tests was to detect any haematological or biochemical complications of the drug.

Results

Eight out of the 100 children enrolled in the study were either excluded because they absconded or were discharged early or the data were insufficient. Thus, 92 patients were available for analysis. Of the 92 patients, 48 were in the isoprinosine group and 44 were in the placebo group. The age and sex distribution in the two groups were similar. The two groups were also comparable in nutritional status and the number of patients admitted with complications. Of the 48 patients in the treatment group, six were classified as mild, 26 as moderate and 16 as severe. These figures are similar to those in the placebo group: mild 6, moderate 22 and severe 16.

Response to treatment

Clinical Course

The clinical course was rated as good or very good in 41 (85%) of 48 patients treated with isoprinosine, (Table) compared with 31 (70%) of 44 patients in the placebo group. The difference was not statistically significant ($p > 0.05$). Although the percentage of patients with poor response to treatment was higher in the placebo group (7/44=16%) than in the isoprinosine group (4/48=8%), the difference was not statistically significant ($p > 0.1$). When the clinical course of only severe cases of measles was analysed, the number of patients with good or very good response in the treatment group (10 out of 14) was similar to the number in the placebo group (10 out of 16).

TABLE

Response of Children with Measles treated with Isoprinosine or Placebo

Grading of response	*Very Good*	*Good*	*Fair*	*Poor*	*Bad*	*Total*
Clinical response						
Isoprinosine	20	21	3	4	0	48
Placebo	16	15	2	7	4	44
Temperature response						
Isoprinosine	14	15	8	3	0	40
Placebo	10	11	4	5	0	30

Temperature Response

Only 70 patients had admission temperature of 38°C and above, although the remaining patients subsequently developed such a temperature. Of the 70 patients, 40 were in the isoprinosine group and 30 in the placebo group. In the isoprinosine group, 29 of the 40 patients (73%) had good or very good response. This response was not different from the 70% (21 out of 30) obtained in the placebo group. Only three patients (8%) in the isoprinosine group had poor response, in contrast to five (17%) of 30 patients in the placebo group. The difference was not statistically significant.

Mortality

All the four deaths occurred in the placebo group, giving a placebo mortality rate of 9% and an overall mortality rate of 4%. Three of the four patients who died had severe measles, while the fourth one had moderately severe disease.

Laboratory tests. There was no significant difference in laboratory results between isoprinosine and placebo patients. In general, the values obtained at discharge, were lower than on admission. Details of laboratory results are being reported separately.

Drug toxicity. Both isoprinosine and the placebo were well tolerated. There was no evidence of acute clinical, haematological or biochemical toxicity.

Discussion

Although patients treated with isoprinosine appeared to have done better than patients treated with placebo, the difference in response of the two groups of patients was not statistically significant. However, it is noteworthy that all the four deaths occurred in the placebo group.

There are few reports on the use of isoprinosine in the treatment of acute measles. In a clinical trial involving 200 patients in Congo, Brazzaville, with 100 patients on isoprinosine and 100 patients on placebo, Samba-Lefebvre[18] reported good or very good results in 58% of patients treated with isoprinosine compared with 43% in the placebo group. The difference between the two groups of patients was statistically significant. There was also significant difference in the mortality rates. The mortality rate was 3% in the isoprinosine group and 7% in the placebo group. The author

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found that the better results in the isoprinosine group occurred in patients with complicated measles and in simple, uncomplicated cases. Gallais *et al*[17] carried out a double-blind clinical trial of isoprinosine in 200 cases of measles in Ivory Coast. Although there was a better response in patients on isoprinosine, the difference between the treatment and placebo groups was not statistically significant. However, the 6% mortality in the isoprinosine group was significantly lower than the 15% in the placebo group. Their results are similar to the findings in the present study.

The initial enthusiasm for isoprinosine as a broad spectrum antiviral agent with immunomodulatory properties is not supported by controlled clinical trials.[4] Further controlled studies are required to define those viral diseases and diseases associated with immunosuppression in which isoprinosine will be of therapeutic value. In measles, apart from reducing the mortality, the drug does not appear to affect the clinical course of the disease. It appears reasonable to restrict further clinical trials of isoprinosine in measles to only severe cases of the disease. The drug was well tolerated and there was no evidence of acute toxicity. However, there is no information about its long-term effects in human beings.

Effective immunization programme with a potent, stable measles vaccine remains the most cost-effective and cost-beneficial method of dealing with measles.

Acknowledgements

We are grateful to Delalande Laboratories (Cedex, France) and Pharbek Chemicals Limited, Ikeja, Nigeria, for supplying the drugs; to our colleagues for allowing us to enroll their patients in the study and to the nursing staff of Emergency Paediatric Unit for their cooperation.

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Accepted 20 December 1982.