SIDE-EFFECTS OF ISOPRODIAN COMPARED WITH WHO-MDT IN RURAL NEPAL

Sir,

In the past, we have used Isoprodian (ISO) (which is a combination preparation containing 50 mg DDS, 175 mg prothionamide and 150 mg isoniazide per tablet), fairly extensively as an anti-leprosy treatment in our field programme, both with and without rifampicin 600 mg on clinic visits, so we thought that detailing our experience with the use of ISO might be of some use to your readers.

The problem we face in Nepal is patients who live too far away from their treatment unit to attend monthly or even bi-monthly for WHO-MDT, so they usually remained on DDS monotherapy. In the past quite a few patients have been treated with ISO, apparently without many problems. So in 1989, when we were considering what to do with the 'monotherapy problem', we considered ISO as a possible alternative for 'remote patients'. However, because a recent study on long-term compliance with prothionamide suggested that only 50% of the doses may be ingested due to the gastro-intestinal side-effects (GIS) of the drug,[1] we decided that we should first try to study the occurrence of any side-effects in Nepali patients before using ISO on a large scale. A study was set up in our Ghorahi referral centre that included patients who had previously been on DDS monotherapy because they lived too far away and any new patients who registered during the study period (1989).

Methodology

In total 106 cases were admitted to the study. Their mean age was 38 (range 11–74, Standard Deviation (SD) = 14·3): 90 were male, 16 were female; 87 patients were classified as MB, 19 as PB. The criteria for MB/PB classification have been discussed at length in reference 2. In all, 37 cases had

Table 1. MB/PB classification of study patients

Classification	Isoprodian	WHO MDT	Total
MB	40	47	87
PB	3	16	19
Total	43	63	106

been previously treated with DDS monotherapy (average duration 58 months, SD = 47 months) and the remaining 69 were new, previously untreated cases. The patients ($n = 63$) that could be motivated to attend the clinic at least once every 2 months were put on WHO-MDT according to their MB/PB classification. The remaining 43 (40·6%) were put on an ISO regimen according to their classification as follows (Table 1):

* PB: Isoprodian 2 od for 1 year.
* MB: Isoprodian 2 od, clofazimine 50 mg od and rifampicin 900 mg stat (supervised) at every clinic visit, for 3 years.

In the ISO group the patients had to walk an average of 23 hours (SD = 17·9) to get to the clinic; in the WHO-MDT group this average was 13 hours (SD = 10·8). At every clinic visit patients had a blood sample taken for PGL-1 serology (on filterpaper), and a DDS urine spot test was done. Patients were examined for signs of jaundice and asked about symptoms of GIS. Patients with a recent history of jaundice, a positive bilirubin urine test, indications of renal failure or gastric ulcer and all pregnant women were excluded from the study. Patients with a positive stool test for parasites received appropriate treatment. Patients were instructed to take their ISO tablets at bedtime with food.

Results

At the time of this evaluation, after an average follow-up time of $3\frac{1}{2}$ years, 14 patients (32·5%) in the ISO treatment group and 13 patients (20·7%) in the WHO-MDT group were lost to follow-up (Figure 1). Of the remaining patients, 32 have been released from treatment and 46 continue on treatment. Of 226 DDS urine spot tests that were done to monitor treatment compliance, 79 (35%) were negative, 1 was doubtful and 147 were positive. There was no difference between the 2 treatment groups in the proportion of tests that were negative ($p = 0{\cdot}7$, χ^2 test), (Figure 2).

During 262 follow-up examinations no episodes of jaundice were found. No mention was made of GID during these examinations, except for 5 patients in the ISO group who had to stop taking Isoprodian due to severe GIS; 4 patients were changed over successfully to a regimen that did not contain prothionamide or isoniazid; 1 patient defaulted after stopping ISO due to severe GIS and 1 patient in the WHO-MDT group finished 24 doses of MB-MDT despite recurrent abdominal pain and nausea. The Relative Risk of developing severe (= persistant, despite symptomatic treatment) GIS when taking Isoprodian as compared to WHO-MDT is 7·33 (95% confidence limits: 0·89–60·53, $p = 0{\cdot}039$, 2-tailed Fisher's exact test).

Discussion

For patients unable to attend regularly for supervised WHO-MDT, Isoprodian seems an attractive alternative. It combines 2 effective anti-leprosy drugs conveniently in 1 tablet. The possible gastro-intestinal side-effects of prothionamide are well known and the risk of hepatitis has especially been found to be dose-related.[3] This may explain why doses of 125 mg and 250 mg daily were found to be acceptable to Indian patients by Stanley *et al.*[4] The same group of investigators found symptoms of 'moderate or severe GIS' in 'a third of the patients' in a compliance study using Isoprodian

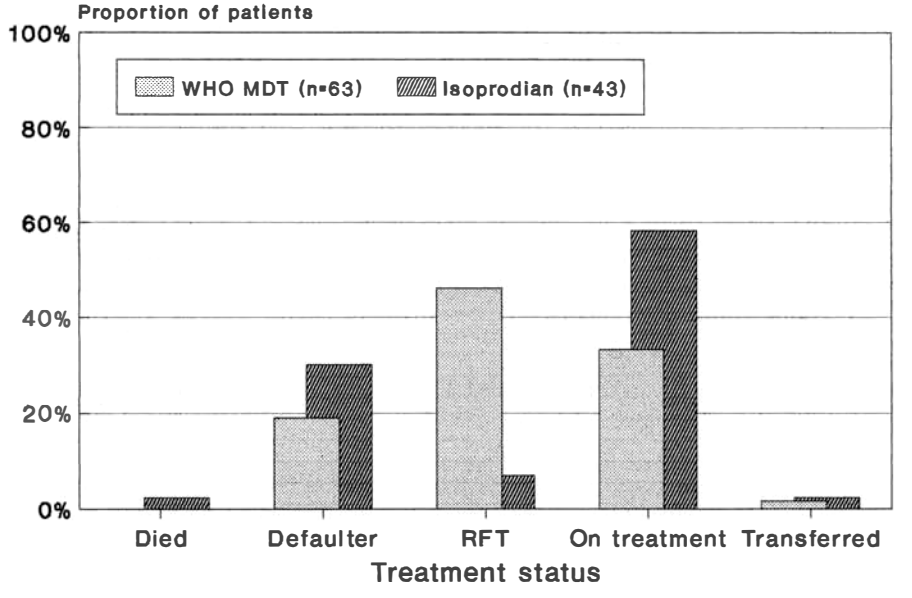

Figure 1. Treatment status of study patients after $3\frac{1}{2}$ years follow-up.

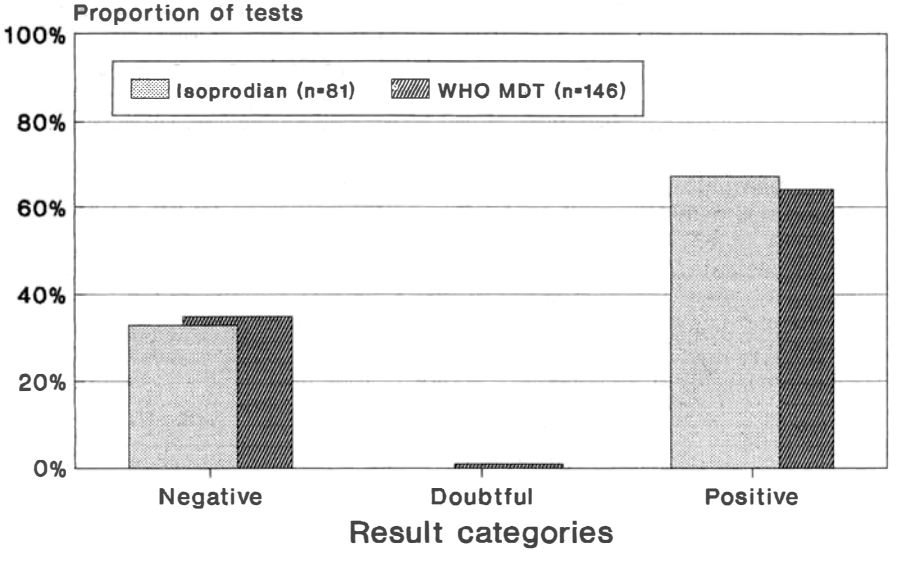

Figure 2. DDS urine spot-test results.

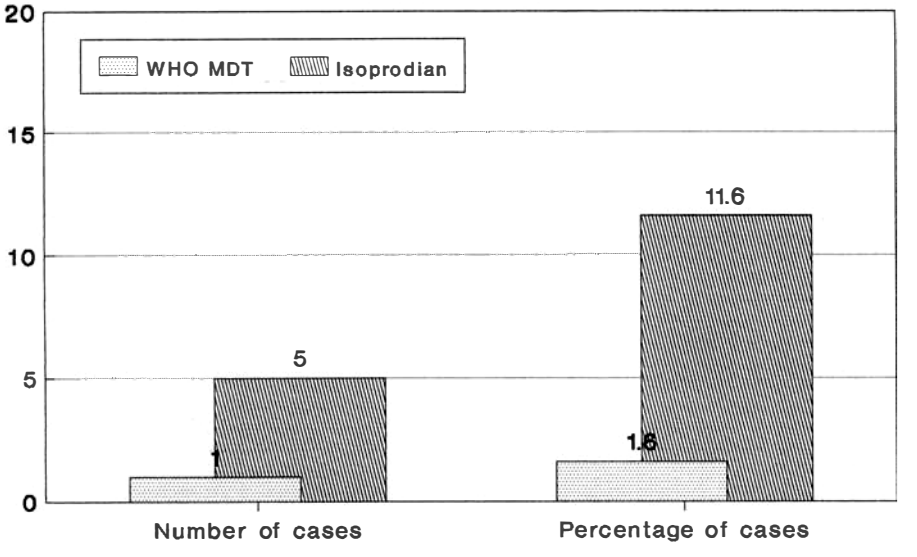

Figure 3. Gastro-intestinal side-effects (severe).

(prothionamide 350 mg daily).[1] GIS appeared to be responsible for the fact that 25% of the patients failed to complete the study. It could well be that this is also the explanation for the high drop-out rate (25%) in this study, but no definite conclusions can be drawn as the defaulter rate was high in both treatment groups and none of the defaulters could be followed up by home visits. The high defaulter rate is, in our experience, quite common among patients living far away from the clinic they attend. In 5 patients (9·3%) of the ISO group the regimen needed to be changed due to severe GIS. These patients were changed over to WHO-MDT, but with rifampicin only at clinic visits, but 1 patient defaulted before the alternative treatment could be started. There is no explanation as to why mild or moderate GIS was not reported. The low compliance of 65% found with the DDS spot test did not seem related to ingestion of prothionamide, as it was similar in both treatment groups.

This study seems to confirm the recommendation of Ellard *et al.*[1] that prothionamide (Isoprodian) should be prescribed only to patients who can be properly monitored. We have decided to treat patients who can not frequently attend the clinic with unsupervised WHO-MDT in blister calendar packs rather than with Isoprodian.

Acknowledgements

We are much indebted to Sr Pennie Thompson and the staff of Ghorahi clinic for the extra work they have done to make this study possible and to Khem Bahadur Gurung for the data entry.

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