Case Report

"FLU" SYNDROME ASSOCIATED WITH OTHER SYSTEMIC MANIFESTATIONS WITH ONCE A MONTH RIFAMPICIN IN THE TREATMENT OF MULTIBACILLARY LEPROSY

A Thomas, P Joseph and R Prabhakar

Rifampicin, a potent bactericidal drug, has become an essential component of multidrug treatment regimens for tuberculosis and leprosy. One of the adverse reactions described following twice weekly or once weekly administration of rifampicin is the "'Flu" syndrome (Sister Mary Aquinas et al 1972, Girling & Wallace 1971). This syndrome is immunological in nature and is often associated with the presence of circulating rifampicin - dependent anti-bodies (Riska & Mattson 1972, Proceedings of Workshop 1973). Initially it was thought to be uncommon with longer intervals between doses of the drug, i.e., once a month administration, as advocated in the chemotherapy of leprosy (WHO 1982). However, there have been a few reports about the occurrence of "Flu" syndrome with a regimen containing rifampicin once a mouth (Naafs & Matemera 1986, Parking & Shah 1989, Patki et al 1988, Vaz et al 1989). We report here three cases of leprosy developing "Flu" syndrome, associated with other systemic manifestations, during the monthly phase of their treatment

CASE REPORTS

CASE 1

A 45-year old male suffering from subpolar lepromatous leprosy with a bacterial index (BI) of 3.67 was prescribed a regimen of rifampicin, clofazimine and dapsone. Rifampicin 600 mg was given daily for three months, twice a week from the fourth to 12th month and once a month from 13 to 24 months. During the monthly phase the patient gave the history that after the second monthly dose of rifampicin, he had developed fever with severe chills and rigors, malaise, giddiness, vomiting and diarrhoea. The above mentioned symptoms appeared approximately one and half to two hours after the administration of drugs and gradually subsided by 24 hours.

Dr A Thomas
Dr P Joseph
* Dr R Prabhakar
Tuberculosis Research Centre, Spurtank Road, Madras 600 031.
* Correspondence and reprint requests

This recurred after the the third and fourth monthly dose also. However, the patient reported this problem to the treating physician only after the fourth monthly dose. In the clinic, the patient was observed after administration of rifampicin under supervision in the same dosage. The temperature was recorded as 98.4° F before giving the drug. After one and half hours he developed chills, rigors and giddiness. His temperature rose to 99.4° F accompanied by severe body ache and vomiting. The patient was given a corticosteroid preparation (Decadron•) and the antihistamine pheneramine maleate, which resulted in the subsidence of symptoms. Rifampicin was terminated and the treatment was continued with clofazimine and dapsone, and the patient's progress then onwards was uneventful.

CASE 2

A female aged 40 years suffering from borderline lepromatous leprosy with a BI of 4.50 was prescribed a regimen of rifampicin, clofazimine, dapsone and pyrazinamide. Rifampicin was given in a dosage of 450 mg, and the scheme of administration was similar to that for case I. She also complained of fever with chills and rigors associated with severe body ache and diarrhoea after approximately one and half to two hours of the monthly dose of rifampicin. The first episode was reported to have occurred after the fourth monthly dose of rifampicin. The symptoms recurred in the following month also but, she had not reported them as she did not associate the problem with ingestion of the drug. She absented herself for the next two months (sixth and seventh month). When she attended for the eighth monthly treatment, rifampicin was administered and the following day she was hospitalised. She was diagnosed as having viral hepatitis and was treated for the same. Her liver function test (LFT) results were as follows: total bilirubin 3 mg/dl, AST 160 units/ml, ALT 120 units/ml and bile pigment was found in the urine. She was discharged after a week.

The LFT was repeated subsequently and the values were within normal limits. It was after the tenth monthly dose of rifampicin when she again developed fever with chills and rigors and diarrhoea and again she had reported to the clinic for the same, that a diagnosis of "Flu" syndrome was made. Rifampicin was immediately withdrawn.

CASE 3

A 25-year old male suffering from subpolar lepromatous leprosy with BI of 4.67 was prescribed the above mentioned regimen and dosage scheme was as for case I. After having the ninth monthly dose of rifampicin the patient

developed fever and vomiting lasting for a few hours on the same day, followed by oliguria of 48 hours duration. The patient attended the clinic on the third day. On examination the patient appeared pale with a haemoglobin level of 10 gm%. His blood pressure was 150/90mm Hg. He was passing dark coloured urine and clinical pathology examination revealed trace of albumin with one to three pus cells/high power field along with RBCs and a large number of hyaline and epithelial casts. Blood urea and creatinine values were 220mg/dl and 13 mg/dl, respectively. On questioning, the patient gave a history of pyrexial attacks for the past four to five months and the fever used to come about two hours after rifampicin administration. Since he used to get better by the same evening he never reported the matter to the clinic. After two days of the latest episode the blood urea and creatinine values were 226mg/dl and 16 mg/dl, respectively, but the patient was feeling better symptomatically. The patient's urine output increased by fourth day. He was admitted in a nephrology ward and was treated on conservative lines. After two weeks his blood urea and creatinine levels had decreased considerably, to 66 mg/dl and 1.3 mg/dl, respectively. In view of his symptoms suggestive of "Flu" syndrome, administration of rifampicin was terminated. The patient was being treated for ENL reaction also and his reaction was brought under control with steroids.

A total of 40 cases were being treated with the above mentioned rhythm of rifampicin of which three patients developed "Flu" syndrome.

COMMENTS

Rifampicin, a powerful bactericidal drug, was introduced in the treatment of tuberculosis in the late sixties. Intermittent administration of rifampicin was initiated around 1969, and a new type of reaction was reported (Poole et al 1971) which was termed 'systemic reaction' and its association with rifampicin antibody formation was discovered subsequently (Poole et al 1971, Riska & Mattson 1972. Proceedings of Workshop 1973). This was followed by reports by various workers (Girling & Wallace 1971, Mattson 1973. Sister Mary Aquinas et al 1972) describing various syndromes such as "Flu" syndrome, abdominal syndrome, respiratory syndrome, cutaneous syndrome and haemolytic syndrome, all associated with intermittent rifampicin administration.

Various animal experiments followed by clinical trials showed that in the

chemotherapy of leprosy, rifampicin administered once month was as effective as daily, twice a week, or, once a week administration of the drug (Levy et al 1976). "Flu" syndrome was not reported in the earlier period of multidrug therapy (MDT) with once a month regimen of rifampicin (Opromolla et al 1981, Girdhar & Dcsikan 1979, Girling & Hitze 1979, Languillon et al 1979, WHO 1982). However. since then a few workers have reported its occurrence even with the administration of once a month rifampicin (Naafs & Matemera 1986, Parking & Shah 1989, Patki et al 1988, Vaz et al 1989).

It has been reported that a higher dosage (900-1200 mg) of rifampicin given intermittently precipitated "Flu" syndrome (Girling & Hitze 1979, Pujet et al 1974, Sister Mary Aquinas et al 1972) and that reduction of dosage to 450-600 mg resulted in disappearance of symptoms. In the present series, the patients were receiving rifampicin 12 mg/kg body weight from the beginning, which amounted to a flat dose of 450-600 mg and yet they developed symptoms suggestive of "Flu" syndrome in association with other systemic manifestations. Similarly, it has also been reported that "Flu" syndrome was was common if intermittent rifampicin administration was preceded by a period of daily administration (Hong Koug Tuberculosis Treatment Services 1974, Vaz et al 1989). However, all the three of our patients who developed "Flu" syndrome had in fact received daily rifampicin for three months before the intermittent administration of the drug was intiated. "Flu" syndrome as has been described by several workers (Patki et al 1988, Vaz et al 1989) is not usually serious enough to warrant termination of rifampicin, since it can be controlled with analgesics and antipyretics. In our experience, as illustrated in these three cases, the syndrome could manifest with more systemic features (abdominal, hepatic reaction, renal failure) which may on occasions be life threatening, warranting termination of rifampicin. Various recent reports (Naafs & Matemera 1986, Parking & Shah 1989, Patki et al 1988, Vaz et al 1989) have shown that monthly dose of rifampicin is not completely free from side effects and it is evident that the medical and the paramedical workers in the field should be aware of this fact while treating leprosy patients with MDT in the programme.

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