

ADVANTAGES AND DISADVANTAGES OF FIXED DOSE COMBINATIONS IN THE TREATMENT OF LEPROSY

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The treatment of leprosy has seen many changes since the days of the chaulmoogra oil. With the synthesis of Dapsone in 1908 a new era in the management of leprosy started. The newer drugs used in the treatment of leprosy include aminoglycosides, dyes, macrolides, rifamycins, enzyme inhibitors, quinolones and immuno-modulators. Multi-drug therapy (MDT) was introduced in 1971 with the idea that it would reduce the incidence of drug resistance and duration of therapy. An action team was set up to monitor the MDT programme in 1981. It was also hoped that the MDT would improve patient compliance. But patient compliance continued to be a problem. Some pharmaceutical firms felt that if the drugs were given as fixed dose combinations, the patient compliance would be better still.

Drug resistant strains have emerged, posing a threat to the pharmacotherapy of leprosy.

Though effective drugs are available, one of the problems to the management of leprosy has been that some clinicians have advocated the use of fixed dose combinations in leprosy management.

I. A FIXED DOSE COMBINATION (FDC)

Drug refers to the combination of drugs in a single pharmaceutical formulation. It does not refer to concomitant drug therapy as multidrug therapy in leprosy, when different drugs are given separately to obtain increased therapeutic range. It should not be confused with the Fixed Duration Therapy (FDT) where the WHO recommended 2 years treatment with MDT for multibacillary patients and 6-month therapy for paucibacillary patients.

II. THE MAJOR ADVANTAGES OF SUCH COMBINATIONS are :

1. *Convenience with improved patient compliance*, specially when two or more drugs are given at a constant dose on a long-term basis. The fewer the tablets that the patient has to take the more reliably he will use them, spe-

cially in the elderly patients who as a group tend to receive more drugs because they have multiple pathology. Separate intake of the individual components of the combination would be too much to ask of the patient with mutilated hands who would be unable to take the tablets out of the blister packs. There is also no certainty that the patient is taking the drugs.

2. *Enhanced effect*, causing a delay or decrease in the incidence of drug resistance and an improvement in the clinical improvement. Combining Isoniazid with Prothionamide and Dapsone ensures that single treatment cannot occur, treatment has to be with all or none of the drugs.
3. *Minimisation of unwanted effects*, where because the drugs are given in a fixed dose combination the dosage of either drug can be reduced and drug synergism can be demonstrated.

III. However THE DISADVANTAGES OF SUCH COMBINATIONS should be

also viewed seriously, specially in the light of the disease being treated.

1. In a fixed dose combination the dose of one drug cannot be decreased without lowering the dose of the other constituent drugs in the preparation. Individualisation of therapy becomes difficult. For example, since Rifampicin and Isoniazid are present in Rimactazid in a ratio which makes it impossible for both components to be administered in a dosage appropriate for children, Rimactazid is not suitable for paediatric use. The same would apply for Isoprodian and Isoprodian-RMP also. Concomitant administration of Clofazimine with Rifampicin may decrease the absorption of Rifampicin. Concurrent administration of Rifampicin with INH may lead to a higher incidence of hepatotoxicity. Dapsone can decrease the anti-inflammatory effect of Clofazimine. Coadministration of clofazimine with Isoniazid may decrease the skin concentration of clofazimine.
2. It is also impracticable for the industry to pro-

vide individualised multi-drug therapy because of the amount of labour involved in the preparation of such combinations.

3. Time course of drug action of the different constituents often demands different intervals between administrations.
4. Differences in the timing of the drug administration may be required for different drugs, such as Rifampicin given early morning on an empty stomach and clofazimine given after a fatty meal and dapsone after a meal.
5. The most difficult problem lies in identifying the cause of a drug reaction if a fixed dose combination is administered. For example, if signs of hypersensitivity appear with Rimactazid, it should be withdrawn and the causal connection with either Rifampicin or Isoniazid determined. The component responsible for the hypersensitivity must then be replaced by another anti-leprotic agent. Similarly, in lepromatous patients with impaired renal function, Isoniazid in Isoprodian should be used with caution. Further, the hepatic damage with a combination of Prothionamide, Rifampicin and Isoniazid can be irreversible.

The most common adverse effects of Dapsone include methaemoglobinaemia, anaemia, psychosis, peripheral neuropathy, hepatitis and photosensitivity apart from an allergic skin rash.

Prothionamide is known to cause dose-related gastro-intestinal effects such as nausea, vomiting, anorexia, excessive salivation, a metallic taste, abdominal pain and diarrhoea.

It can also cause hepatotoxicity which is more severe in the presence of Rifampicin. The drug also causes psychosis, anxiety, depression, postural hypotension, hypoglycemia, hypothyroidism and hypersensitivity.

Rifampicin occasionally can produce pseudomembranous enterocolitis and hepatotoxicity, apart from it being an enzyme inducer. The drug also causes leucopenia, occasionally hemolytic anemia, ataxia, dizziness, visual disturbances and occasionally renal failure.

Clofazimine causes discoloration and ichthyosis of the skin, discoloration of sweat, tears and urine, gastrointestinal upsets with abdominal pain, hypokalemia generalised lymphad-

enopathy, pedal oedema and occasionally peripheral neuritis.

Ofloxacin commonly causes nausea, vomiting, diarrhoea, abdominal pain, rarely pseudomembranous enterocolitis, tremors, drowsiness, insomnia, nightmares, visual disturbances, hallucinations, psychosis, depression, convulsions, peripheral neuropathy, premature epiphyseal closure and hypersensitivity.

Isoniazid is well known to cause neuritis, hepatitis, anaemia, hyperglycemia, gastrointestinal disturbances, and convulsions. These are more common in slow acetylators in whom the rate of metabolism is slower and therefore the drug accumulates.

6. In the case of drug resistance it would be difficult to determine to which drug the patient has developed resistance. The viability of *M. leprae* in the skin and peripheral nerves even 2 years after MDT in multibacillary patients has been reported⁽¹⁾
7. Pharmaceutical companies may find fixed dose combinations more in demand. The promotional methods of the industry are good in presenting the material selected in such a calculated way as to encourage the use of the drugs in question. Poor prescribing may then result from an inaccessibility of information.

IV. Fixed dose combinations tried in the management of leprosy :

1. Hydrosulfone, a fixed dose combination of hydnocarpus extract with dapsone, was administered as an injection, but compliance was poor as it was extremely painful. Over the last decade other fixed dose combinations have been developed for the management of leprosy.
2. Isoprodian : This contains Isoniazid + Prothionamide + Dapsone. The role of Isoniazid is questionable because it is claimed to be ineffective, if not harmful, in leprosy.
3. Isoprodian + Rifampicin has also been tried in a few centres. The addition of Rifampicin is synergistic with Isoniazid.
4. Dapsomine : This contains Dapsone 100 mg + Clofazimine 100 mg and was expected to make compliance better in multidrug leprosy. However in patients in whom clofazimine is used to treat Type II reactions, a high dose of

dapsone could be antagonistic.

5. Disulone is a combination of Dapsone with ferrous oxalate. It is presumed that the ferrous oxalate will correct the anaemia caused by Dapsone. However, this anaemia is of the hemolytic type and not of the microcytic and hypochromic nature.
6. Cotrifazide : This contains Rifampicin 115 mg + Cotrimoxazole 320 mg +
7. Isoniazid 80 mg. Studies done in 1988 showed that between 80 and 90% of patients treated with this combination showed clinical cure within a two month period. Patients with complications of leprosy at the start of the treatment are better treated with cotrifazide. It is claimed to have practically no side effects. It is also claimed that if the patient develops any other infection while he is on this drug, no alternative antibiotic is required. Emdetine: This contains Rifampicin 115 mg + Cotrimoxazole 320 mg + Prothionamide 375 mg. Its effect is claimed to be equal to that of cotrifazide.
8. Combination of Rifampicin 150 mg + Isoniazid 87.5 mg + Dapsone 50 mg + Ofloxacin 150 mg has been quite effective. It is suggested that Ofloxacin, a fluorinated quinolone drug, can even replace Prothionamide. It is well tolerated and has a wide spectrum of activity.
9. Combination of Brodimoprim, a dihydrofolate reductase inhibitor akin to trimethoprim, with Dapsone has shown a strong synergistic inhibitory activity.

At the International Leprosy Congress in 1993 Alverenga⁽²⁾ commented that the use of fixed dose combinations in leprosy management improved compliance, but the risk of adverse effects had not been reduced significantly.

A great many marketed preparations are open to criticism. Occasionally an advantage may

be justified in theory but insignificant in practice. Such combinations seem to be marketed to fill a commercial purpose rather than a medical need. But rational combinations are acceptable. Therefore, before prescribing a combination drug, the physician must consider whether the ingredients in the combination are necessary. Can their co-administration affect the kinetics of any of the ingredients? The adverse effects of the drugs that are used in the fixed dose combinations must be borne in mind, with the understanding that combining the drugs can augment and compound the number and intensity of the adverse drug reactions.

Tuberculosis made a virulent come-back at a time when we felt its morbidity no longer alarming. In the same way, we are likely to face a new threat in leprosy. One report from Brazil in June 1996⁽³⁾ shows that the high prevalence of leprosy and the increased trend of HIV infections in the Amazon Basin suggest that the co-existence of these two infections is not a rare event. However, Prof. Lechat of Belgium feels relieved that there is a lack of association between HIV infection and leprosy⁽⁴⁾. Is this a premature confidence or an expression of faith?

Dr. Noordeen's comment in the International Journal of Leprosy, December 1995 is quite valid: Currently we have no tools to completely interrupt transmission, neither do we have dependable tools to measure the transmission of infection⁽⁵⁾.

In CONCLUSION we must not forget that we still have not broken the riddle of the lepra bacillus. Though the lepra bacillus was the first microbe to be identified, it has posed a challenge to research since the days of Gregor Armeur Hansen. We cannot afford to fan the fantasies of pharmaceutical industries or the fancies of the clinician.

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