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# Prospective Study on the Relationship Between Intensive Bactericidal Therapy and Leprosy Reactions[1]

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In the past, dapsone (DDS) has been considered to be a cause of reactions during the treatment of leprosy. Nowadays many leprologists fear that the use of strong bactericidal drugs such as rifampin (RMP) will increase the risk and severity of reactions. Pfaltzgraff even suggests that RMP should only be used very sparingly and should be reserved for highly bacilliferous patients ([17]). Such worries are based on theoretical considerations and anecdotal evidence. In the leprosy services of Kisangani and Musienene, Zaire, a systematic study was performed on the relationship between the appearance of reactions and RMP given in different dosages.

## PATIENTS AND METHODS

All cases of leprosy with signs of active disease, whether previously treated or not, are taken into therapeutic trials. Patients are examined clinically by experienced leprosy workers, skin smears from three body sites are performed, and the bacterial index (BI) following the Ridley scale is determined. Skin smears are examined locally, and regularly, for quality control, a second smear is taken and sent to the Leprosy Laboratory, Institute of Tropical Medicine, Antwerp, Belgium. A biopsy for histopathological confirmation of the diagnosis is taken, and also examined in Antwerp.

For the purpose of this trial, the patients were divided into two groups: paucibacillary (PB) cases with a BI of $<2$ at any site examined, and multibacillary (MB) cases with a BI of $\geq 2$ at any site.

Treatment regimens were as follows (RMP = rifampin; ETH = ethionamide; DDS = dapsone; CLO = clofazimine):

**Paucibacillary cases.** Regimen A: 1 dose of RMP 1500 mg (supervised) followed by 1 year of daily DDS 100 mg (unsupervised). Regimen B: 10 weekly doses of RMP 900 mg (supervised). Regimen U: 1 single dose of RMP 40 mg/kg body weight (supervised).

From 1 May 1982 to 31 May 1983, PB cases were randomly allocated to treatment groups A or B, if they were willing to present themselves weekly at the center for ten weeks. If not, they were given treatment A. From 1 June 1983 onward, all PB cases were randomly allocated to treatment groups A or U.

**Multibacillary cases.** Regimen C: 6 months daily RMP 600 mg + ETH 500 mg + DDS or CLO 100 mg (supervised) followed by 6 months daily DDS or CLO 100 mg (unsupervised). Regimen D: the first 6 months same as C (supervised) followed by 6 months of daily ETH 500 mg + DDS or CLO 100 mg (unsupervised). In Musienene, the daily dose of ETH was reduced to 250 mg in the later phase of the study. WHO-MB regimen: 2 years of once-monthly supervised RMP 600 mg + CLO 300 mg, with daily unsupervised DDS 100 mg + CLO 50 mg.

MB patients living near the center, or accepting to be hospitalized for six months (accessible patients) were allocated to regimens C or D. All female patients and all male patients treated for more than five years with DDS monotherapy were randomized between regimens C or D but always taking CLO as the third drug. Male patients treated for less than five years with DDS monotherapy were randomized between regimens C and D but with DDS as the third drug. To determine previous treatment, it was nec-

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essary to rely on the history. No records of old patients were available. DDS has been the only drug used in the area, and its administration was often sporadic and in insufficient dosage.

Patients who were inaccessible for intensive daily treatment but for whom monthly supervision could be guaranteed were given the WHO multibacillary treatment regimen.

For children with a body weight under 30 kg, the dosages of RMP were adapted as follows: 1500 mg = 25 mg/kg body weight; 900 mg = 15 mg/kg body weight; 600 mg = 10 mg/kg body weight.

After completion of treatment, the patients were given placebo tablets and were invited to present themselves monthly or once every two months at the center. Although some patients failed to show up regularly, most of them were seen at least six times a year.

Reactions were diagnosed clinically, and all data entered on the individual records of the patients. The present study takes into consideration those reactions the patient was subjectively complaining about, i.e., the patient spontaneously presented at the center or complained of pain at the time of a routine examination. Inflammation of one or more nerves and/or inflammation of existing skin lesions and/or peripheral edema were considered to be diagnostic criteria of type 1 reactions. Erythema nodosum leprosum (ENL) was diagnosed when typical skin manifestations and/or iridocyclitis and/or orchitis were present. Since it may be difficult, especially in BL cases, to distinguish between type 1 and ENL reactions, in those cases ENL was excluded when the reaction failed to respond to thalidomide, or when a biopsy showed no signs of ENL. Silent neuritis was not included. The reactions were graded as mild, moderate, or severe, taking into consideration the severity of the clinical symptoms and the kind of treatment needed to bring the reaction under control.

For type 1 reactions, treatment was routinely started with acetylsalicylic acid (ASA) 3.0 g daily, sometimes together with chloroquine 600 mg daily. If no improvement occurred within three days, corticotherapy was started with dexamethasone 6 mg daily, and continued as long as necessary while gradually reducing the daily dose. The duration of corticotherapy was not standardized, but adapted to each individual. The duration varied from six weeks to six months. However, it was not always possible to adhere to this scheme. The patients are ambulatory, and some failed to show up for control three days after the start of ASA. It may be that they felt better, or it may be that they were too ill to come. Moreover, corticotherapy is always given under supervision, meaning that the patient has to be hospitalized, which may be refused, or has to present daily at the center, which he may fail to do.

ENL reactions were also treated with ASA. If no improvement occurred, thalidomide was given, except to women of childbearing age who received a short course of corticotherapy. Because of the availability of alternative effective treatments, clofazimine was not used for the treatment of reactions since this drug has an antibacterial activity against *Mycobacterium leprae,* and could thus influence the bacteriological results of the therapeutic trials.

Levels of significance were calculated with the $\chi^2$-test or with Fisher's exact test.

## RESULTS

### Reactions among paucibacillary patients

Table 1 shows the number and proportion of reactions among the 335 PB patients. Since there was no significant difference between males and females or between adults and children, these are grouped together. The overall incidence of reactions is 6%. There are significantly more reactions in regimen B than in the two other regimens.

Table 2 shows the clinical pattern of these reactions. Most reactions were mild or moderate in severity and responded well to ASA or no treatment at all; severe reactions were equally distributed among the three groups. Half of the reactions involved a single nerve. Group B showed more reaction episodes, and polyneuritis and peripheral edema were also more frequent in group B.

A detailed analysis did not reveal any high risk age group. Previous treatment had no influence on the frequency of reactions. The mean and median of the first reactional ep-

TABLE 1. *Reactions in paucibacillary patients in the different treatment regimens.*[a]

| | Treatment regimens | | | Totals |
|---|---|---|---|---|
| | A | B | U | |
| Total no. patients | 184 | 59 | 92 | 335 |
| No. patients with reactions | 4 | 11 | 5 | 20 |
| Percentage with reactions | 2.2% | 18.6% | 5.4% | 6.0% |

[a] A vs. B, $p < 0.001$.
U vs. B, $p < 0.002$.
A + U vs. B, $p < 0.001$.

isode was the same in all three groups, with large individual variations (between 1 and 37 weeks). The rather large proportion of reactions of four weeks' duration was due to the monthly interval of the clinical examinations. Treatment for mild to moderate reactions is ambulatory, and when the patient is seen four weeks later and the symptoms have disappeared the duration is noted as four weeks, although in reality it might be shorter. The mean duration of the reactional episodes was shortest in group B, probably because of a few very long reactional episodes in the other groups; the median is comparable in the three groups.

### Reactions among multibacillary patients

**Type 1, upgrading reactions.** Table 3 shows the number of type 1 reactions among MB patients. Since there was no significant difference in the rates between children and

TABLE 2. *Clinical features of the paucibacillary reactions.*

| Regimens | No. episodes | Onset[a] | Duration (weeks) | Symptoms[b] | Severity[c] | Treatment[d] |
|---|---|---|---|---|---|---|
| A | 1 | 5 | 18 | L | M | — |
| | 1 | 22 | 4 | 1 | L | — |
| | 1 | 32 | 5 | 1 | L | ASA |
| | 1 | 25 | 28 | P | S | DEX |
| | Mean | 16.8 | 12.2 | | | |
| | Median | 22–32 | 5–18 | | | |
| U | 1 | 16 | 4 | 1 | M | ASA |
| | 1 | 23 | 1 | O | M | ASA |
| | 1 | 18 | 12 | L | M | — |
| | 2 | 4 | 4 + 4 | 1 + 1 | L + L | — + ASA |
| | 1 | 10 | 7 | 1 | S | DEX |
| | Mean | 16.25 | 5.4 | | | |
| | Median | 16 | 4 | | | |
| B | 1 | 35 | 40 | P, L | M | ASA |
| | 1 | 12 | 4 | P | L | ASA |
| | 1 | 1 | 1 | 1 | M | ASA |
| | 1 | 35 | 2 | 1 | S | DEX |
| | 1 | 37 | 3 | 1 | M | ASA |
| | 1 | 7 | 4 | O | M | ASA |
| | 2 | 4 | 4 + 4 | L + 1 | L + L | — + ASA |
| | 1 | 27 | 39 | P | M | DEX, ASA |
| | 1 | 9 | 26 | L | L | — |
| | 4 | 4 | 4 + 4 + 4 + 4 | 1 + 1 + 1 + 1 | M + L + L + L | ASA + — + — + ASA |
| | 3 | 11 | 3 + 12 + 4 | O, P + P + O | S + M + M | DEX + DEX + ASA |
| | Mean | 16.2 | 10.0 | | | |
| | Median | 11 | 4 | | | |

[a] Onset = number of weeks after starting treatment (first episode).
[b] 1 = single nerve involvement; P = polyneuritis; L = inflammation of skin lesions; O = peripheral edema.
[c] L = light; M = moderate; S = severe.
[d] — = none; ASA = acetylsalicylic acid; DEX = dexamethasone.

TABLE 3. *Reactions in multibacillary patients in the different treatment regimens.*

| | Treatment regimens | | |
|---|---|---|---|
| | C | D | WHO-MB |
| Total no. patients | 129 | 128 | 23 |
| No. patients with type 1 reactions | 71 | 58 | 4 |
| Percentage with type 1 | 55% | 45% | 17% |
| No. patients with ENL | 14 | 20 | 0 |
| Percentage with ENL | 11% | 16% | 0% |

TABLE 5. *Upgrading reactions in patients receiving treatments C or D and either DDS or CLO as third drug.*

| Sex | Third drug | Total | Reactions | Percent |
|---|---|---|---|---|
| Males | DDS (a) | 74 | 45 | 60 |
| | CLO (b) | 102 | 43 | 42 |
| Females | CLO (c) | 81 | 41 | 50 |

DDS in males (a) vs. CLO in males (b), $p = 0.02$.
DDS in males (a) vs. CLO in males (b) plus CLO in females (c), $0.02 < p < 0.05$.

adults or between males and females, these groups were not separated. Since there was no significant difference in the incidence of type 1 reactions between regimens C and D, and both regimens contain the same dosages of the bactericidal drugs RMP and ETH, they were also considered together.

The WHO-MB regimen gives rise to considerably less type 1 reactions ($p < 0.001$). Previously untreated patients developed significantly more type 1 reactions than patients treated previously. This merits in-depth investigation, but exact data on the duration, regularity, and dosage of previous treatment of the patients in this study are unavailable. The reaction risk is also significantly correlated with age and BI; more patients aged 15–44 with a BI $\geq 5$ developed a reaction than did older patients or patients with a lower BI (data not shown).

Table 4 summarizes the clinical features of the reactions for each treatment group. The paucibacillary reactions are also included since the pathogenesis of upgrading reactions in both PB and MB leprosy is thought to be identical. Type 1 reactions in the C + D group were more frequent and appeared significantly earlier ($p < 0.001$) than in the other groups. Two patients died during a reactional episode of unrelated causes; one of heart decompensation, the second of hepatitis. Another patient died at home of an unknown cause one week after a reaction had subsided.

In contrast with paucibacillary type 1 reactions, which present either as neuritis or

TABLE 4. *Clinical features of all reactions according to treatment regimens.*

| | Total no. patients | No. with reactions | Onset[a] | | Duration[b] | Reactional episodes[c] | | Symptoms[d] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mean | Median | | Total no. | Mean | L | P | O | 1 |
| C + D, type 1 | 257 | 129 50% | 9.7 | 5 | 9 | 226 | 1.8 | 58% | 25% | 54% | 11% |
| C + D, ENL | 257 | 34 13% | 17.4 | 13 | 8.5 | 97 | 2.9 | 26.5% neuritis 2.9% orchitis 8.8% iridocyclitis | | | |
| WHO-MB, type 1 | 23 | 4 17% | 22 | 25.5 | 13.6 | 4 | 1.0 | 75% | 50% | 0% | 25% |
| PB (A + U) | 276 | 9 3% | 17.2 | 18 | 8.7 | 10 | 1.1 | 20% | 10% | 10% | 60% |
| PB (B) | 59 | 11 18% | 16.2 | 11 | 10.0 | 17 | 1.5 | 17% | 29% | 17% | 47% |

[a] Onset of first reaction = weeks after starting treatment.
[b] Mean duration in weeks.
[c] Total number in each group; mean number per patient.
[d] Symptoms expressed as a percentage of all reactions: L = inflammation of skin lesions; P = polyneuritis; O = peripheral edema; 1 = single nerve involvement.

TABLE 6. *Evolution of nerve swelling between start of therapy and last follow-up examination.*

| Change in nerve swelling | Paucibacillary | | | Multibacillary | |
|---|---|---|---|---|---|
| | A No. (%) | B No. (%) | U No. (%) | C + D No. (%) | WHO-MB No. (%) |
| −1 | 16 (8.6) | 5 (8.5) | 10 (10.8) | 22 (8.5) | 3 (13.0) |
| −2 | 6 (3.2) | 2 (3.4) | 8 (8.6) | 43 (16.7) | 2 (8.6) |
| −3 | 5 (2.7) | 3 (5.0) | 2 (2.1) | 14 (5.4) | 1 (4.3) |
| −4 | 6 (3.2) | 2 (3.4) | 4 (4.3) | 22 (8.5) | 1 (4.3) |
| −5 | 3 (1.6) | — | 2 (2.1) | 8 (3.1) | — |
| −5 | 2 (1.0) | 1 | — | 23 (8.9) | — |
| Total with decreased swelling | 38 (20.3) | 13 (20.3) | 26 (18.9) | 132 (51.1) | 7 (30.2) |
| Unchanged | 100 (54.3) | 38 (64.4) | 48 (52.1) | 70 (27.2) | 11 (47.8) |
| +1 | 18 (9.7) | 2 (3.4) | 9 (9.7) | 20 (7.7) | 2 (8.6) |
| +2 | 16 (8.6) | 4 (6.7) | 8 (8.6) | 18 (7.0) | — |
| +3 | 3 (1.6) | 1 (1.7) | — | 4 (1.5) | 1 (4.3) |
| +4 | 3 (1.6) | — | — | 9 (3.5) | 1 (4.3) |
| +5 | 3 (1.6) | — | — | — | 1 (4.3) |
| +5 | 3 (1.6) | 1 (1.7) | 1 (1.0) | 4 (1.5) | — |
| Total with increased swelling | 46 (24.7) | 8 (13.5) | 18 (19.3) | 55 (21.2) | 5 (21.5) |

inflammation of the skin lesions or peripheral edema, multibacillary patients frequently present several of these symptoms at the same time. This tendency is even more pronounced in severe reactions. Peripheral edema is a very common feature of type 1 reactions in multibacillary patients.

As shown in Table 5, there were significantly less type 1 reactions in the patients who received CLO as a third drug. Patients who received a reduced dose of ETH did not develop less reactions. DDS or CLO as the third drug did not influence the frequency of severe reactions. On the other hand with regard to severe reactions, the patients receiving CLO had fewer reactions, they began later, and they were of shorter duration.

**ENL.** ENL was much less frequent than type 1 reactions (Table 3), and males developed more ENL reactions than females (data not shown). There were no significant differences between regimens C and D, while the incidence of ENL was the same whether DDS or CLO constituted the third drug. Patients who received a reduced dose of ETH developed marginally less ENL ($p = 0.047$, data not shown). Clinical features are included in Table 4.

**Permanent nerve damage.** Nerve damage has been evaluated by two parameters: a) changes in nerve thickness and b) in disabilities. In Table 6, the decrease or increase in the thickness in 1 to 5 or more nerves between the start of treatment and the last examination is shown for each treatment

TABLE 7. *Number of deformity scores changing by 2 or more units between first and last examination.*[a]

| Change in nerve | Paucibacillary | | | Multibacillary | |
|---|---|---|---|---|---|
| | A No. (%) | B No. (%) | U No. (%) | C + D No. (%) | WHO-MB No. (%) |
| +2 | 27 (2.4) | 11 (3.1) | 13 (2.3) | 50 (3.2) | 2 (1.4) |
| +3 | 7 (0.6) | — | 1 (0.1) | 7 (0.5) | — |
| −2 | 24 (2) | 2 (0.5) | 7 (1.2) | 46 (2.9) | 5 (3.6) |
| Unchanged | 1046 (94.7) | 341 (96.3) | 531 (96.1) | 1439 (93.3) | 138 (94.9) |

[a] Each patient has 6 deformity scores.

regimen. Improvements and deteriorations in PB patients were approximately equal. The proportion of PB patients ending up with a number of nerves unchanged in thickness compared with their status at the start of therapy was highest among treatment group B. In MB patients, both regimens C + D and WHO-MB showed more nerves decreasing than increasing in thickness, but the proportion of improving patients was greater in the C + D group, the final result, in terms of the proportion of patients with more thickened nerves at the final examination, being equal. It would thus seem that most reactions are of a transient nature.

Table 7 shows the number of deformity scores (WHO scoring system) that changed by 2 or 3 units between the start of treatment and the last examination. Overall, about 3% of the scores showed a deterioration of 2 or 3 units, without any regimen differing significantly from the others.

## DISCUSSION

The significantly higher number of upgrading reactions observed among paucibacillary patients treated with regimen B as compared with regimens A and U is an argument in favor of the hypothesis that a more aggressive bactericidal regimen causes more reactions. In regimen A, patients received 1500 mg of rifampin; in regimen U, 2000 mg (for an adult of 50 kg); in regimen B, 9000 mg. However, besides the total dosage of rifampin administered, two other parameters should be envisaged: a) the peak serum concentrations reached in the different regimens, and b) the frequency of these peak serum concentrations. The highest peak serum concentrations should be reached in regimen U followed by A and B, with reiterations only in the latter. On the basis of the observations made, it is impossible to decide which factor is responsible for the higher incidence of reversal reactions in regimen B, the higher total amount of drug administered or the reiterated peak serum concentrations.

It could be argued that the higher incidence of type 1 reactions in group B was caused by the more frequent contacts of that group with the leprosy workers; during the first ten weeks of treatment, patients in group B were seen every week, while the patients in groups A and U were usually seen only every month or every two months. However from the tenth week after the start of treatment, contact frequency was the same for all three groups. Thus, for reactions starting after week 10 the three groups are more comparable.

Table 2 shows that the onset of the first reaction episode took place after more than ten weeks for 3 out of 4 reactions in group A, 6 out of 11 reactions in group B, and 4 out of 5 reactions in group U. Although a higher proportion of reactions during the first ten weeks is noted in group B, this difference is not significant. The comparison of the figures for reactions starting after more than ten weeks (3/183 for A, 6/54 for B, 4/91 for U) shows that there is no difference between A and U ($p = 0.13$), while the difference between A + U and B is still highly significant ($p = 0.009$). Thus the higher reaction incidence in group B was not caused by a difference in observer contact. If more reactions occur in regimen B, the incidence of severe reactions is identical to that in the other two regimens. Overall, 14.3% of the reactions were graded as severe.

We may, therefore, conclude that for the regimens studied in the paucibacillary patients, most reactions were mild to moderate and of short duration, that the time of onset was extremely variable, and that the incidence of reactions was higher in regimen B than in regimens A or U, but of equal severity.

MB patients developed more upgrading than ENL reactions and significantly more type 1 reactions than the PB patients ($p < 0.005$). Type 1 reactions were thus not mainly a BT feature. This has also been reported by others ([17]) and illustrates that many MB patients are, in fact, PB cases who have downgraded, probably as a result of lack of treatment. However, the incidences of reversal reactions in the MB-WHO regimen group and in the PB regimen B group are comparable.

Type 1 reactions in MB patients are more severe than in PB patients and start earlier. Their duration was longer in Kisangani than in Musienene, but these patients had more episodes, illustrating local differences. Several symptoms manifested simultaneously,

while peripheral edema was a very frequent symptom. This again may be correlated with the amounts of bactericidal drugs administered: MB-WHO = 7.2 g of RMP in 1 year; PB, group B = 9 g of RMP in 10 weeks; and MB-C + D = 110 g of RMP in 6 months, together with 45 g of ETH (for an adult of 50 kg). However, it is difficult to attribute to RMP an exclusive causative role in reactions. Eighteen patients experienced a reaction before the start of treatment, while 16 reactions in the C + D group appeared after stopping RMP intake at 26 weeks, even as late as week 124, i.e., 98 weeks after stopping RMP. The occurrence of late reversal reactions has been described elsewhere ([3, 13]).

Previously untreated MB patients developed significantly more upgrading reactions as compared with patients treated previously (with DDS). The use of CLO, 100 mg daily, instead of DDS as a third drug in the C and D regimens protects against the appearance of type 1 reactions and makes them less severe. It would be interesting to compare the association of RMP with either DDS or CLO in PB patients to see whether CLO would also reduce the frequency and severity of reactions in PB cases.

Males developed more ENL reactions than females, and no protective effect resulted from the administration of CLO 100 mg/day. A reduction of the dosage of ETH may prevent somewhat the occurrence of ENL.

After the first reports on the possible anti-inflammatory action of CLO in lepromatous leprosy by Browne and Hogerzeil ([2]) and Browne ([1]), other publications on the results of the administration of CLO are rather contradictory. Most authors claim that the drug is very useful in the treatment of ENL ([4, 6–10, 12, 19, 20, 26–28]) or is without effect ([4, 15, 22]). Others claim that CLO acts better in the treatment of reversal reactions ([11, 16, 18, 24]). Others are of the opinion that clofazimine is equally active on reversal reactions and ENL ([5, 12, 21, 25]). The symposium of 1968 ([23]) illustrates the differences of approach of each author in this matter.

The present study was not intended to study the curative effect of CLO on reactions but allows one to conclude that CLO at a dosage of 100 mg daily has a beneficial effect on the prevention of type 1 reactions in MB leprosy although it does not prevent the appearance of ENL.

None of the regimens gave rise to unacceptable permanent nerve damage.

The concern of Pfaltzgraff ([17]) that rifampin may enhance type 1 reactions seems to be confirmed by this study, especially in previously untreated MB patients. However, one does not need to go so far as to advise against its use in all types of leprosy. Pfaltzgraff especially singles out BT and BL cases. But both treatment A (which has shown its efficacy, unpublished results) and treatment U are, so far as reactional complications are concerned, very acceptable in paucibacillary leprosy. Also, the assertion ([17]) that highly bacilliferous patients will suffer less from the reactional effect of rifampin is not validated by the present study.

In terms of both type 1 and ENL reactions, the WHO regimen was superior to regimens C and D. The latter have already been shown to be hepatotoxic ([13]). Alternative effective short-course regimens will have to be tried to avoid these complications while exploiting the potent bactericidal activity of RMP.

## SUMMARY

A systematic study was performed on the reactions occurring during several short-course therapy regimens for the treatment of paucibacillary and multibacillary patients.

Most type 1 upgrading reactions in paucibacillary (PB) leprosy were mild to moderate and of short duration, while the time of onset was extremely variable. Their incidence was higher in the regimen rifampin (RMP) 900 mg once weekly for ten weeks than when a single dose of RMP 40 mg/kg body weight was given or 1500 mg in one dose followed by one year of dapsone (DDS) 100 mg daily.

In multibacilary (MB) leprosy, three regimens were compared: MB-WHO regimen; regimen C, consisting of daily RMP 600 mg, ethionamide (ETH) 500 mg, and DDS or clofazimine (CLO) 100 mg for six months, followed by six months of daily DDS or CLO; and regimen D, identical to regimen C but comprising daily DDS or CLO plus ETH 500 mg during the second semester.

Type 1 upgrading reactions occurred more

frequently in MB patients and were more severe than in PB patients. They occurred more frequently and were more severe in regimens C and D than in the MB-WHO regimen. CLO 100 mg daily prevented type 1 reactions in MB patients and rendered them less severe. ENL was also more frequent in regimens C and D and was not prevented by CLO in the dosage used.

Although there is some correlation between type 1 reactions and the total amount of RMP administered, other aspects of RMP administration, such as serum peak concentration and reiteration of serum peaks, must also be considered when examining the role of RMP in the etiology of reactions. Optimal strategies will have to be developed to best exploit the potent bactericidal activity of RMP.

## RESUMEN

Se hizo un estudio sistemático sobre la ocurrencia de reacciones en pacientes paucibacilares y multibacilares sujetos a varios esquemas de tratamiento de corta duración.

En los pacientes paucibacilares (PB) la mayoría de las reacciones tipo 1 sugerentes de mejoría ("upgrading") fueron moderadas, de corta duración, y con un tiempo de aparición extremadamente variable. Su incidencia fue mayor cuando se administraron 900 mg de rifampina (RMP) una vez por semana durante 10 semanas, que cuando ésta se administró en una sola dosis de 40 mg/kg de peso o de 1500 mg seguida por un año de tratamiento con 100 mg diarios de dapsona.

En la lepra multibacilar (MB) se compararon 3 esquemas de tratamiento: el esquema MB-WHO; el esquema C, consistente en 600 mg diarios de RMP, 500 mg diarios de ethionamida (ETH) y 100 mg de DDS o clofazimina (CLO) durante 6 meses, seguidos por 6 meses de DDS o CLO; y el esquema D, idéntico al esquema C pero adicionado de DDS o CLO más 500 mg de ETH durante el segundo semestre.

Las reacciones "upgrading" del tipo 1 ocurrieron más frecuentemente en los pacientes MB y fueron más severas que en los pacientes PB. También fueron más frecuentes y severas con los esquemas C y D que con el esquema MB-WHO. La CLO a 100 mg diarios evitó las reacciones del tipo 1 en los pacientes MB y las hizo menos severas. El ENL también fue más frecuente con los esquemas C y D y no se evitó por la CLO a la dosis usada.

Aunque hay alguna correlación entre las reacciones del tipo 1 y la cantidad total de RMP administrada, cuando se examina el papel de la RMP en la etiología de las reacciones también deben de considerarse otros aspectos tales como su concentración máxima alcanzada en suero y la frecuencia con la que se alcanzan las concentraciones séricas máximas. Deben desarrollarse otras estrategias para la explotación óptima del potencial bactericida de la RMP.

## RÉSUMÉ

On a procédé à une étude systématique des réactions survenant lors de différents régimes thérapeutiques de courte durée administrés pour le traitement de malades tant paucibacillaires que multibacillaires.

La plupart des réactions de type 1 ("upgrading") chez les malades paucibacillaires (PB) étaient légères ou modérées, et de courte durée. Leur moment d'apparition était extrêmement variable. L'incidence de ces réactions était plus élevée avec un régime à la rifampine (RMP) consistant en 900 mg hebdomadaire pendant dix semaines qu'à la suite d'une dose unique de rifampine à raison de 40 mg/kg de poids corporel, ou de 1500 mg en une dose unique suivie par de la dapsone à la dose de 100 mg par jour pendant un an.

Dans la lèpre multibacillaire (MB), trois posologies ont été comparées, à savoir la posologie multibacillaire recommandée par l'OMS, la posologie C consistant en 600 mg de rifampine quotidienne, 500 mg d'ethionamide (ETH) et de la dapsone ou de la clofazimine (CLO) à raison de 100 mg pendant six mois, suivies de traitement journalier par la dapsone ou la clofazimine; enfin une posologie, identique à la posologie C, mais comprenant en outre l'administration journalière de dapsone ou de clofazimine, accompagnées au cours du deuxième semestre par de l'ethionamide à raison de 500 mg.

Les réactions de type 1 survenaient plus fréquemment chez les malades multibacillaires, elles étaient également plus graves que chez les malades paucibacillaires. Elles sont apparues plus fréquemment, elles étaient plus graves, avec les posologies C et D, qu'avec la posologie recommandée par l'OMS. La clofazimine à raison de 100 mg par jour a empêché l'apparition de réactions de type 1 chez les malades multibacillaires, ou les a rendues moins graves. L'erythème noueux l'épreux (ENL), a également été relevé plus souvent avec les posologies C et D; la clofazimine aux doses utilisées n'a pas permis de le prévenir.

Encore que l'on note une certaine corrélation entre les réactions de type 1 et la quantité totale de rifampine administrée, d'autres aspects de l'administration de rifampine doivent être considérés lorsqu'on étudie le rôle de ce médicament dans l'étiologie des réactions, par exemple, la concentration maximale dans le sérum, et la répétition de tel pic. Il faudra mettre au point une stratégie optimale en vue d'utiliser au mieux l'activité bactéricide puissante de la rifampine.

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