INTERNATIONAL JOURNAL OF LEPROSY

Volume 43, Number 1
Printed in the U.S.A.

Effect of Quinacrine, Chloroquine and Primaquine on the Multiplication of *Mycobacterium leprae* in Mice[1, 2]

Stefaan R. Pattyn and Godelieve Verdoolaeghe-Van Loo[3]

The mechanism of action of dapsone (DDS) is generally thought to be interference in folic acid synthesis through competition with para-aminobenzoic acid (PABA). In a previous study ([8]) it was found that in mycobacteria with increasing resistance for dapsone the competitive action of PABA with DDS was less and less efficient. On the other hand, Shepard ([9]) and ourselves (unpublished results) found that in the mouse model it was difficult to neutralize the action of dapsone on *Mycobacterium leprae* with PABA. Differences in solubility of both substances resulting in differences in penetration into bacterial organisms was proposed as a possible explanation ([9]). However, the possibility must be kept in mind that the activity of dapsone could, at least partly, be situated at other metabolic levels. It is known for instance that sulfonamides besides their competition with PABA also interfere in the direct oxidative pathway for glucose, at the level of glucose-6 phosphate-dehydrogenase. So also does quinacrine ([4]).

We therefore investigated the activity of quinacrine on the multiplication of *M. leprae* in the mouse foot pad model. Because of the complex mode of action of quinacrine, the action on *M. leprae* of two other antimalarials, chloroquine and primaquine, was also tested.

MATERIALS AND METHODS

Methods used were those previously described ([6]). *M. leprae* strain 17547, described previously ([7]) was used. Mice were treated until the controls reached the plateau phase of multiplication. The antimalarials were mixed in the food, which was administered in 5 gm quantities per mouse per day. Dosages were as follows: quinacrine 10 mg and 100 mg per kg body weight; chloroquine 15 mg per kg body weight; primaquine 0.25 mg per kg body weight. Fresh mixtures of the latter were prepared weekly.

RESULTS

As can be seen in Table 1, the low dosage quinacrine was insufficiently active, but the high dosage, 100 mg per kg body weight, completely inhibited the multiplication of *M. leprae.* Its action was, however, purely bacteriostatic; multiplication resumed when treatment was stopped. Chloroquine and primaquine on the other hand were devoid of any bacteriostatic activity against *M. leprae.* These results do not indicate that quinacrine could be used in human treatment since the necessary dosage is too high and its action is purely bacteriostatic. However, there is some theoretical interest in studying the activity of antimalarial drugs on *M. leprae* since dapsone is also active against some forms of malaria parasites.

DISCUSSION

The mode of action of quinacrine is complex. Besides its action on G-6-phosphate dehydrogenase it also inhibits 6-phosphofructokinase in the Embden Mayerhof pathway and binds with DNA and also transfer and ribosomal RNA ([2 3]). Chloroquine is thought to bind with DNA. It also decreases oxygen consumption in many tissues. Primaquine, on the other hand, exerts its action through binding with the mitochondria of the exoerythrocytic forms of malarial parasites. Our results showing that quinacrine inhibits the multiplication of *M. leprae,* while chloroquine and primaquine do not, favor the hypothesis that quinacrine acts on *M. leprae* through the inhibition of the direct oxidative pathway of glucose catabolism.

[1] Received for publication 19 June 1974.

[2] This work was supported by a grant from the Damiaanfonds, Brussels, Belgium.

[3] S. R. Pattyn, M.D., Professor Medical Microbiology, University of Antwerpen, Belgium, and part-time Professor of Tropical Microbiology, Institute for Tropical Medicine, Antwerp, Belgium; G. Verdoolaeghe-Van Loo, Laboratory Technician, Institute for Tropical Medicine, Antwerp, Belgium.

TABLE 1. *Effect of quinacrine on the multiplication of* M. leprae *in mice.*

Treatment	Effect [a]	Without treatment for 6 months
Controls	positive	
Quinacrine 10 mg/kg	6/7	
Quinacrine 100 mg/kg	0/5	4/4
Chloroquine 15 mg/kg	7/7	
Primaquine 0.25 mg/kg	14/15	

[a] Number of mice showing number of AFB comparable with those in the control animals; denominator number of mice examined.

The most important function of this pathway is to furnish NADPH (nucleotide adenosine diphosphate) necessary in the synthesis of fatty acids and steroids.

On the other hand, Cenedella and Saxe ([1]) have pointed out that a possible mechanism of antiplasmodium activity of dapsone could be the inhibition of glucose catabolism of intraerythrocytic *Plasmodium berghei.* There would, thus, be a parallel between the mode of action of dapsone and that of quinacrine. A functioning direct oxidative pathway in *M. leprae* would be in contrast with the situation in *M. phlei* ([5]).

SUMMARY

Quinacrine administered at 100 mg per kg body weight to mice had a bacteriostatic activity on *M. leprae* in the mouse, chloroquine at 15 mg per kg and primaquine at 0.25 mg per kg were without activity. These findings could point to the presence of a functioning direct oxidative pathway of glucose catabolism in *M. leprae.*

RESUMEN

La administración de quinacrina a lauchas en dosis de 100 mg por Kg de peso corporal tuvo acción bacteriostica sobre el *M. leprae,* cloroquina a la dosis de 15 mg y primaquina a la dosis de 0.25 mg por Kg de peso corporal no demostraron actividad. Estos hallazgos sugeririan la presencia de un mecanismo oxidativo directo en el catabolismo glucido del *M. leprae.*

RÉSUMÉ

La quinacrine administrée par voie orale à la dose de 100 mg per kg de poids possède une activité bactériostatique vis à vis *Mycobacterium leprae* chez la souris; la chloroquine, administrée à la dose de 15 mg/kg poids et la primaquine administrée à raison de 0.25 mg/kg de poids n'ont aucun effet. Ces résultats pourraient indiquer la présence du cycle de l'oxydation directe du glucose chez *M. leprae.*

REFERENCES

1. CENEDELLA, R. J. and SAXE, L. H. Partial reversal of the *in vivo* antimalarial activity of DDS against *Plasmodium berghei* by induced hyperglycemia. Am. J. Trop. Med. Hyg. **20** (1971) 530-534.
2. DIPALMA, J. R. *Drill's Pharmacology in Medicine,* 4th edit., New York: McGraw Hill Book Co., 1971, pp 1777-1778.
3. GOODMAN, L. S. and GILMAN, A. *The Pharmacological Basis of Therapeutics,* 4th edit., London-Toronto: The Macmillan Co, 1970, p 1100.
4. HARPER, H. A. *Review of Physiological Chemistry,* Los Altos, Calif.: Lange Medical Publication, 1969, p 255.
5. LE CAM-SAGNIEZ. Métabolisme des glucides chez *Mycobacterium phlei* et *Mycobacterium tuberculosis.* Ann. Soc. Belg. Med. Trop. **53** (1972) 347-354.
6. PATTYN, S. R., ROLLIER, R., ROLLIER, M. R., DE MUYNCK, A., JANSSENS, P. G. and VERDOOLAEGHE-VAN LOO, G. Correlation of laboratory and clinical data during treatment of leprosy. Ann. Soc. Belg. Med. Trop. **52** (1972) 537-548.
7. PATTYN, S. R. and ROOYACKERS, J. Traitement de l'infection expérimentale à *Mycobacterium leprae* chez la souris. Ann. Soc. Belg. Med. Trop. **45** (1965) 27-30.
8. PATTYN, S. R. and VAN ERMENGEM, J. DDS sensitivity of mycobacteria. Antagonistic effect of PABA for *M. ulcerans* and *M. kansasii.* Int. J. Lepr. **36** (1968) 427-431.
9. SHEPARD, C. C. Studies in mice of the action of DDS against *Mycobacterium leprae.* Int. J. Lepr. **35** (1967) 616-622.