Reports on Individual Drugs

Ivermectin in onchocerciasis

For many years diethylcarbamazine and suramin have been the only drugs that have offered any possibility of arresting the progress of onchocerciasis, or river blindness. However, their toxicity and the need for medical supervision of the required multidose regimens renders them unsuitable for mass chemotherapy (see p. 83).

Control of the blackfly has thus far provided the only means of reducing the prevalence of the disease in the areas of most intense transmission. The World Health Organization, through its Onchocerciasis Control Programme, has maintained an extensive spraying campaign within the countries of the Volta River Basin in West Africa since 1974. It is estimated that this has reduced the attack rate by some 80%. However, effective larviciding programmes are impractical in other habitats in which the disease is endemic. Even in the Volta Basin continual invasion by flies from outside the area and the emergence of insecticide-resistant strains have rendered it necessary to extend the treated areas and to introduce new insecticides (1).

It has thus long been recognized that the existing benefits can be maintained only if more effective drugs can be developed; and three research-based pharmaceutical companies which have responded to this challenge are currently assessing candidate compounds. One of these, ivermectin (Merck, Sharp & Dohme), has already been submitted to extensive clinical evaluation in West Africa within a developmental programme involving the collaboration of WHO and the competent governmental authorities. The results, which are particularly encouraging, raise expectation that a preparation will become available for more extensive use within the near future.

Ivermectin, which is derived from one of several macrocyclic lactones produced by an actinomycete *Streptomyces avermitilis* isolated from soil samples in Japan (2), acts by disrupting central neurosynaptic transmission mediated by gamma-aminobutyric acid (3-5). It is well tolerated in mammalian experimental animals, provided it is excluded from penetrating the central nervous system by an effective blood-brain barrier (6), but it is lethal in single low-dose exposure to a variety of nematode and arthropod parasites. However, it has not thus far shown useful activity against trematode or cestode worms.

Its potential in the treatment of human onchocerciasis was suggested by its potent microfilaricidal action in analogous diseases in horses and cattle (7-9). Several studies have since been undertaken to demonstrate the efficacy of the compound as a microfilaricidal agent in man (10-23). These include preliminary dose-ranging studies and subsequent double-blind trials in which ivermectin was compared with diethylcarbamazine and placebo. Collectively, they have involved the administration of ivermectin to more than 1200 adult patients with onchocerciasis of varying severity. The results have been impressively consistent. They demonstrate that ivermectin in a single oral dose of 150 µg/kg rapidly depresses the dermal microfilarial density to a very low level which is maintained for over 12 months and that this is accompanied by a slow clearing of microfilariae from the anterior chamber of the eye. Histological studies of adult female worms suggest that this effect results, at least in part, from impairment of the normal intrauterine development of the microfilariae and inhibition of their release from the uterus (14, 15).

The therapeutic effect is thus more prolonged than that of diethylcarbamazine and, presumably because its microfilaricidal action is less abrupt, its use has thus far not been associated with severe systemic or ocular adverse reactions. Fever, pruritus, tenderness of lymph nodes and mild transient hypotension have been reported in some patients, but these have generally been described as mild, and have rarely required steroid therapy. The

totality of the evidence consequently indicates that a single annual oral dose of ivermectin of the order of 100 μg/kg will be well tolerated by adult patients and will inhibit the symptoms of the disease and preserve imperilled sight. There is even a possibility, in view of its effects on the reproductive apparatus of the female worm, that multiple dosing may result in a macrofilaricidal action. Hope also exists that as a result of sustained depression of the dermal microfilarial density, use of ivermectin on a community scale will reduce the local intensity of transmission of the disease (24, 25).

There is, however, a particular and inevitable need for caution in proposing a new drug for community use. Careful surveillance of many more treated patients will be required before unanticipated rare reactions can be excluded with adequate confidence, and plans for extensive post-marketing surveillance are already in hand. Moreover, ivermectin has been shown to be teratogenic on repeated daily administration to mice at a dose some fivefold higher than the proposed single therapeutic dose. It is also toxic to suckling neonatal rats, which unlike human neonates, do not possess a highly developed blood-brain barrier at birth. Even if the potential for such toxicity exists in human beings, the therapeutic dose is likely to be well below the threshold for its expression. None the less, ivermectin should not, in the current state of knowledge, be administered to pregnant or lactating women or to young children (26). This imposes an important constraint on the use of a drug intended for community treatment and it underscores the need for effective and prolonged post-marketing surveillance.

Despite this important reservation, ivermectin remains a compound of outstanding promise. It is encouraging that Merck, Sharp & Dohme is continuing to support investigation of its potential in other parasitic diseases. This has recently been rewarded by preliminary clinical findings that, in the same dosage, it exerts a potent, but less prolonged microfilaricidal effect in bancroftian filariasis (27), a disease that affects some 80 million people in tropical and subtropical regions (28).

References

1. *WHO Independent Commission on the Long-Term Prospects of the Onchocerciasis Control Programme. Final Report.* i-xi, 1-77. Geneva, World Health Organization (1981).
2. Campbell, W. C. et al. Ivermectin: a potent new antiparasitic agent. *Science,* **221**: 823-828 (1983).
3. Campbell, W. C. Ivermectin: An Update. *Parasitology Today,* **I**: 10-16 (1985).
4. Wang C. C. & Pon, S. S. Actions of avermectin B_{1a} on GABA nerves. *Progress in Clinical and Biological Research,* **97**: 373-395 (1982).
5. Terada, M. et al. *Angiostrongylus cantonensis.* Paralysis due to avermectin B_{1a} and ivermectin. *Experimental Parasitology,* **57**: 149-157 (1984).
6. Pulliam, J. D. et al. Investigating ivermectin toxicity in collies. *Veterinary Medicine,* **80**: 33-40 (1985).
7. Egarton, J. R. et al. The antiparasitic activity of ivermectin in horses. *Veterinary Parasitology,* **8**: 83-88 (1981).
8. Klei, T. R. et al. Efficacy of ivermectin (22, 23-dihydroavermectin B_1) against adult *Setaria equina* and microfilariae of *Onchocerca cervicalis* in ponies. *Journal of Parasitology,* **66**: 859-861 (1980).
9. Campbell, W. C. Efficacy of the avermectins against filarial parasites: a short review. *Veterinary Research Communications,* **5**: 251-262 (1982).
10. Aziz, M. A. et al. Efficacy and tolerance of ivermectin in human onchocerciasis. *Lancet,* **2**: 171-173 (1982).
11. Aziz, M. A. et al. Ivermectin in onchocerciasis. *Lancet,* **2**: 1456-1457 (1982).
12. Coulaud, J. P. et al. Ivermectin in onchocerciasis. *Lancet,* **2**: 526-527 (1984).
13. Awadzi, K. et al. Ivermectin in onchocerciasis. *Lancet,* **2**: 921 (1984).
14. Awadzi, K. et al. The chemotherapy of onchocerciasis. An assessment of four single dose treatment regimens of MK-933 (ivermectin) in human onchocerciasis. *Annals of Tropical Medicine and Parasitology,* **79**: 63-78 (1985).
15. Schulz-Key, H. et al. Treatment of human onchocerciasis: the efficacy of ivermectin on the parasite. *Tropical Medicine Parasitology,* **36**: 20 (1985).
16. Lariviere, M. et al. Double-blind study of ivermectin and diethylcarbamazine in African onchocerciasis patients with ocular involvement. *Lancet,* **2**: 174-177 (1985).
17. Dadzie, K. Y. et al. Ocular findings in a double-blind study of ivermectin vs diethylcarbamazine vs placebo in the treatment of onchocerciasis. *British Journal of Ophthalmology,* **71**: 78-85 (1987).
18. Greene, B. M. et al. Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis.

New England Journal of Medicine, **313**: 133-138 (1985).
19. Awadzi, K. et al. The chemotherapy of onchocerciasis. A double-blind comparative study of ivermectin, diethylcarbamazine and placebo in human onchocerciasis in Northern Ghana. *Annals of Tropical Medicine and Parasitology,* **80**: 433-442 (1986).
20. Diallo, S. et al. A double-blind comparison of the efficacy and safety of ivermectin and diethylcarbamazine in a placebo-controlled study of Senegalese patients with onchocerciasis. *Transactions of the Royal Society of Tropical Medicine & Hygiene,* **80**: 927-934 (1986).
21. Taylor, H. R. et al. Treatment of onchocerciasis: Comparison of the ocular effects of ivermectin and diethylcarbamazine. *Ophthalmology,* **104**: 863-870 (1986).
22. Campbell, W. C. & Benz, G. W. Ivermectin: A review of efficacy and safety. *Journal of Veterinary Pharmacology and Therapeutics,* **7**: 1-16 (1984).
23. White, A. et al. Controlled trial and dose-finding study of ivermectin for treatment of onchocerciasis. *Tropical Medicine and Parasitology,* **47**: 96 (1986).
24. Cupp, E. W. et al. The effects of ivermectin and diethylcarbamazine on the transmission of *Onchocerca volvulus,* the causative agent of "river blindness". *Science,* **231**: 740-742 (1986).
25. Bissan, Y. & Ranque, P. The effect of ivermectin (MK-933) on the transmission of *Onchocerca volvulus* by *Simulium sirbanum* in the Sudan-Savannah zone of Mali. *Proceedings of the 10th Meeting of the WHO Scientific Working Group on Filariasis.* Bamako, Mali, November 5-9, 1984.
26. Aziz, M. A. Chemotherapeutic approach to control of onchocerciasis. *Review of infectious diseases,* **8**: 500-504 (1986)..
27. Diallo, S. et al. Dose-ranging study of ivermectin in treatment of filariasis due to *Wuchereria bancrofti. Lancet,* **1**: 1030 (1987).
28. WHO Technical Report Series, No. 702, 1984 (*Lymphatic filariasis:* fourth report of the Expert Committee).