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Received 24 July 1986; revised 6 June 1988; accepted for publication 30 June 1988

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (1988) 82, 867

Short Report

Arteether, a qinghaosu derivative, in toxoplasmosis

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Toxoplasmic encephalitis is a common and life-threatening occurrence in patients with acquired immunodeficiency syndrome (AIDS). The current treatment of choice is the combination of pyrimethamine and sulfadiazine. This combination, however, while being highly effective against the disease, has the inconvenience of being associated with a high incidence of side effects which often require withdrawal of therapy. Therefore, there is an urgent need for newer and safer therapy for this disease.

Arteether is an ethyl ether derivative of qinghaosu (QHS) (BROSSI *et al.*, 1988). QHS is a naturally occurring sesquiterpene lactone which has been isolated from the traditional Chinese herb *Artemisia annua* (KLAYMAN, 1985), the structure of which includes a peroxide ring. QHS has been found active in *in vitro* and *in vivo* models against *Plasmodium* (PETERS *et al.*, 1986), and *in vitro* against *Naegleria fowleri* (COOKE *et al.*, 1987). Interestingly, QHS crosses the blood-brain barrier and is also effective against cerebral malaria (LI *et al.*, 1984). Because *Toxoplasma gondii* is also a protozoon, we tested the activity of QHS against this parasite using an *in vitro* and *in vivo* model. Unelicited mouse peritoneal macrophages were used to test the anti-*Toxoplasma* activity of arteether as previously described (CHANG & PECHÈRE, 1988). Macrophage monolayers were infected with *T. gondii* for 1 h, washed twice, and incubated for 18 h with media containing arteether in concentrations from 0·01 to 400 μg/ml. Preliminary results suggested that arteether had some inhibitory effect on *Toxoplasma* replication by diminishing the number of infected cells and the number of *Toxoplasma* per 100 cells in concentrations as low as 0·1 μg/ml. Further experiments showed, however, that these results were not reproducible. We have no explanation for this, as these macrophages were obtained from pathogen-free and *Toxoplasma* serologically negative mice. Moreover, arteether exerted no inhibitory activity on the incorporation of [^{3}H]uracil by intracellular *T. gondii* in concentrations from 0·01 to 400 μg/ml. We emphasize, therefore, that both systems are complementary and must be used together, when possible, for assessing the *in vitro* activity of compounds against *T. gondii*.

Swiss-Webster female mice were infected intraperitoneally with 5×10^3 tachyzoites of the highly virulent RH strain of *T. gondii* (CHANG & PECHÈRE, 1987). 24 h later, arteether was administered subcutaneously at daily doses of 1, 10, 25, 50, 100, 200, 400 and 600 mg/kg for 5 d. All untreated control mice died 7±1 d after challenge, as did all mice treated with up to 100 mg/kg. With 200 mg/kg there was an increase in survival, 20% of mice living until the 15th day after challenge, but all died of toxoplasmosis on the 16th day, as demonstrated by autopsy. Mice treated with 400 and 600 mg/kg, however, presented acute signs of toxicity after the 2nd day of therapy. Therapy was therefore stopped on this day, and all the mice receiving 400 mg/kg died 10 d after challenge; all those receiving 600 mg/kg died 4 d after challenge. As positive controls, infected mice were treated orally with 330 mg/kg of roxithromycin for 5 d (SD_{50}=336 mg/kg×5 d; CHANG & PECHÈRE, 1987), which afforded 71·4% protection, or with A-56268, a new macrolide, at a dose of 300 mg/kg for 9 d, which afforded 100% protection (CHANG *et al.*, 1988).

The results of this investigation suggest that arteether would not be useful in the treatment of toxoplasmosis.

Acknowledgements

This work was supported in part by grant 3·221-085 from the Fonds National Suisse de la Recherche Scientifique.

We thank the World Health Organization Scientific Working Group on the Chemotherapy of Malaria for the supply of arteether, which was synthesized on its behalf by Dr P. Buchs, SAPEC SA, Barbengo, Lugano, Switzerland.

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Received 23 May 1988; revised 14 June 1988; accepted for publication 30 June 1988