TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, VOL. 76, NO. 4, 1982

Bioavailability and tolerability of mebendazole in patients with inoperable hydatid disease

A. D. M. BRYCESON[1], R. WOESTENBORGHS[2], M. MICHIELS[2] AND H. VAN DEN BOSSCHE[3]
[1]*Hospital for Tropical Diseases, London NW1 0PE;* [2]*Dept. of Drug Metabolism and* [3]*Dept. of Comparative Biochemistry, Janssen Pharmaceutica, B-2340 Beerse, Belgium*

Mebendazole has been used for the treatment of human hydatid disease for more than five years. Little information, however, is available on levels of drug in the sera or cyst fluid of patients. Although mebendazole is poorly absorbed from the gut (BRUGMANS *et al.*, 1971) one might expect the results of therapy to be related to these levels.

Blood samples for estimation of mebendazole were taken at weekly intervals for four weeks, and fortnightly thereafter, from nine patients with inoperable hydatid disease treated with 40 to 200 mg/kg/day for between 12 and 48 weeks. The drug was taken in three divided doses eight-hourly with a snack which contained fat. Treatment was not supervised unless the patient was in hospital for surgery or rehabilitation. Mebendazole was given as tablets of 100 mg, until 500 mg became available at the end of 1979. In two volunteers the two formulations were found to give comparable levels. In two volunteers and in two patients treated for filariasis peak levels were found one to three hours after intake. Serum was separated the same day from 10 ml clotted blood samples, stored at −20°C and transported on dry ice to Janssen Pharmaceutica, Beerse, Belgium, for radioimmunoassay.

Patients were questioned for side-effects and examined weekly for four weeks, then every two weeks. Haemoglobin, leucocytes, platelets, aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin, serum proteins, urea, creatinine and electrolytes were measured at each visit. Urine was examined for sugar, protein and casts. All patients tolerated the tablets. In two, transaminases were temporarily increased. Although mebendazole was maintained the enzyme activity returned to normal within four to six weeks. No other abnormalities occurred.

Table I shows means and ranges of mebendazole serum levels one to three hours after administration in the nine individual patients. From 24 observations made in seven subjects during treatment with 40 to 60 mg/kg/day, serum levels remained below 90 ng/ml. By contrast, concentrations exceeded this value on 14 occasions when determined from four patients

Table I—Mean (and range) of serum mebendazole levels estimated in 9 patients with hydatid disease from samples taken 1-3 h after oral intake. The total daily doses shown were administered in 3 divided doses given 8-hourly.

Patients' initials	ng/ml		
	40-60 mg/kg/day	100-150 mg/kg/day	200 mg/kg/day
RM	36 n=1	55 n=1	87 (55-173) n=13
TL	79 (74-88) n=3		
NZ	44 (9-90) n=5	40 (18-53) n=3	43 (18-58) n=12
KD	50 (24-76) n=2		18*(14-20) n=3
LM	77 (71-81) n=2	106 (99-112) n=2	131 (111-164) n=8
SM	64 (31-84) n=4		
MV	33 (7-55) n=7		
SR			65 (39-93) n=11
RH			258 (220-297) n=2

*Peak levels of 128 and 84 ng/ml were recorded 5 h and 9 h after dosing respectively.
n = the number of observations from which the data were obtained.

during treatment with 200 mg/kg/day. These subjects' maximum attained values were 93, 164, 173, 297 ng/ml, respectively. Analysis of cerebrospinal fluid from one patient receiving 200 mg/kg/day gave concentration of 8·6 ng/ml (maximum attained serum level was 93 ng/ml).

Throughout the study there was considerable within patient variation in one to three hour serum levels, but low concentrations were observed consistently eight hours after intake. In one patient (LM) serum levels clearly rose with dosage, in two others the relationship was not so clear while in a fourth (KD) levels bore so little relationship to dose or time as to suggest poor compliance.

Because of the heterogeneity of patients with respect to the site, severity and manifestations of disease, no definite conclusions could be drawn about the relationship between serum levels and clinical response. However, there was strong indirect evidence of a successful response in three individuals with extensive hydatid disease who consistently attained 3-hour serum levels in excess of 100 ng/ml whilst undergoing treatment with 1/3 × 200 mg/kg mebendazole eight-hourly. These patients are reported in detail elsewhere (BRYCESON *et al.*, 1982). The considerable difficulties experienced in assessing the results of chemotherapy suggest that formal clinical trials will need careful planning. None the less limited trials designed to answer specific questions and controlled by estimations of serum levels are now indicated.

References

Brugmans, J. P., Thienpont, D. C., Van Wijngaarden, I., Vanparijs, O. F., Schuermans, V. L. & Lauwers, H. L. (1971). Mebendazole in enterobiasis. Radiochemical and pilot clinical study in 1,278 subjects. *Journal of the American Medical Association*, **217**, 313.

Bryceson, A. D. M., Cowie, A. G. A., MacLeod, E., White, S. Edwards, D., Smyth, J. D. & McManus, D. P. (1982). Experience with mebendazole in the treatment of inoperable hydatid disease in England. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **76**, 510-518.

Accepted for publication 26th April, 1982.