EVALUATION OF A HIGH DOSE METOCLOPRAMIDE INFUSION REGIMEN

E.M. McGovern, S.M. Bryson, F. Wilson, A.W. Kelman, G.J. Addis and B. Whiting
Departments of Pharmacy, Materia Medica and Nuclear Medicine, Stobhill General Hospital, Glasgow, G21 3UW.

The pharmacokinetic parameters of metoclopramide (MTC) have previously been determined in a group of nineteen patients with bronchial carcinoma (Bryson et al, 1985). From these data, MTC clearance was related to body weight (Cl = 0.33 L/h/kg; Eq.1) and was significantly correlated with serum urea (Cl = 0.57 - [0.036 x urea mmol/L]; Eq.2).

In the present study, a further six patients received MTC by infusion in the form of a loading dose of 3.6 mg/kg/0.5 h followed by a maintenance dose of 3.6 mg/kg/10h. The validity of the two clearance equations for the prediction of average steady state MTC concentrations was compared (Cp = Infusion rate x Clearance), and the safety and efficacy of the regimen was assessed.

The patients were aged 48 to 70 years (mean 59), and their weights ranged from 33.2 to 99.1 kg (mean 55). Each patient received single agent cyclophosphamide (CCP) in a dose of 2.5 G/m^2 given over two hours commencing concurrently with the maintenance MTC infusion.

Blood samples were collected immediately after the loading infusion and after 3, 6 and 10 hours of maintenance infusion. These were analysed by HPLC (Bryson et al, 1984) to determine the average steady state concentration (C). This was compared in each case with two predicted average concentrations (Cp_1 based on Eq.1 and Cp_2 based on Eq.2) by means of a prediction error ($PE_1 = Cp_1 - C$) and $PE_2 = Cp_2 - C$). Statistical analysis with the Student's unpaired t test was employed to test for the presence of bias, with the Null Hypothesis stating that the mean prediction error is not significantly different from zero. To compare the forecasting precision of the two equations, the F ratio test was applied to differentiate between the variances of groups PE_1 and PE_2. Therapeutic effect was assessed objectively by emesis counts and subjectively by the patient using visual analogue scales for degree of nausea and appetite suppression. Patients were closely monitored for adverse effects.

The mean prediction errors (±SD) were + 0.02 ± 0.50 µg/ml and -0.1± 0.37 µg/ml for PE_1 and PE_2 respectively; neither clearance equation was associated with biased predictions. The variance of group PE_2 was smaller than PE_1, although not to an extent which was statistically significant.

Therapeutic success (defined as normal food intake, absence of significant nausea and a maximum of 2 episodes of emesis in the 24 hours following CCP) was achieved in all but one patient receiving MTC prophylaxis against chemotherapy with a strong emetic component. This patient had a C of 0.83 µg/ml in comparison to an observed range of 0.7 - 1.8 µg/ml. The only noticeable side effect was sedation which was mild to moderate in three patients; in particular, no evidence of dopamine antagonist activity was seen.

Initial findings from this investigation encourage the individual selection of MTC infusion regimens which aim for a minimum of 1 µg/ml on the basis of clearance Eq.2.

Bryson, S.M. et al (1985) Br. J. Clin. Pharmacol. (in press)
Bryson, S.M. et al (1984) J. Clin. Hosp. Pharm. 9: 263-266.