A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL FOR ABSORPTION OF ORAL PARACETAMOL IN MAN

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In conventional pharmacokinetic models of drug absorption of orally-administered preparations the gastrointestinal tract is commonly treated as a single entity. This is clearly at variance with the physiological structure of the gastrointestinal tract and recent studies have shown that gastric emptying rate is an important determinant of absorption of drugs such as paracetamol (Nimmo and others, 1975).

We propose a model to describe the kinetics of absorption of orally-administered paracetamol in man with separate compartments representing the stomach and small intestine. Absorption (first-order) was assumed to occur only from the small intestine with subsequent distribution into conventional central and peripheral body compartments.

Paracetamol solution (20mg/kg) containing ^{113m}In diethyltriamine pentaacetic acid (DTPA) (300μCi) as a non-absorbable isotopic marker was ingested by healthy fasting subjects. The gastric emptying pattern was obtained from the serial scintiscans of the abdomen (Heading and others, 1971). Frequent blood samples were taken concurrently and paracetamol concentrations in plasma were measured by g.l.c. (Prescott, 1971). In repeat studies in some subjects pethidine (150mg) or pentazocine (60mg) was given intramuscularly 30 min prior to ingesting the paracetamol and isotope solution. Only 6 of 19 studies showed a single monoexponential gastric emptying pattern (Type I). In eight studies there was a very fast initial emptying of the solution followed by monoexponential emptying of the remainder (Type II). Other studies showed two periods of monoexponential emptying separated by a quiescent interval (Type III). Plasma paracetamol concentration data were analysed by the proposed model and (where possible) by the conventional model using non-linear optimisation (Nelder & Mead, 1965). In all cases the proposed model gave good agreement between measured and calculated values, and yielded an estimate of the rate constant (K_A^*) for absorption from the small intestine; the mean half-time for absorption was 6.8 ± 0.9 (s.d.) mins.

Overall, there was no correlation between the gastric emptying rate constant (K_G) during the exponential phase and the apparent absorption rate constant (K_A) for the conventional model (Figure 1). However, these variables were approximately equal in value where Type I emptying was observed. As expected K_A^* was larger than either K_A or K_G and there was no statistically significant correlation between K_A^* and K_A. The apparent absorption rate constant K_A is therefore a hybrid constant and cannot be used to calculate either K_A^* or K_G.

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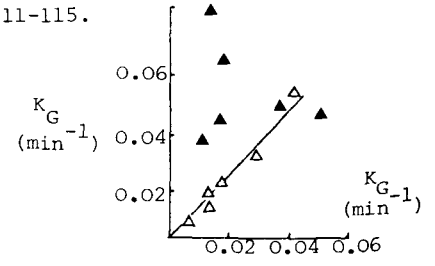

Fig. 1. Apparent absorption rate constant (K_A) vs. gastric emptying rate constant (K_G) for Type I (△) and Type II (▲) emptying patterns.