

Comparative pharmacokinetics of Panadol Extend® and immediate-release paracetamol metabolites.

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ABSTRACT

Background:

Panadol Extend (PEX) is an over-the-counter, sustained-release formulation of paracetamol. Each 665mg tablet contains 69% slow release and 31% immediate release paracetamol. In a previous simulated human overdose study, PEX exhibited lower and later peak serum concentrations and a lower area under the curve (AUC) than comparable doses of immediate-release paracetamol (APAP-IR)¹. It is uncertain whether the lower AUC resulted from incomplete absorption of paracetamol or metabolism occurring simultaneously with absorption.

Objective:

To assess whether differences in pharmacokinetics (PK) between PEX and APAP-IR result from incomplete absorption or simultaneous absorption and metabolism by comparison of paracetamol metabolite recovery in a human simulated overdose model.

Methods:

PEX or APAP-IR administered at 80 mg/kg to nine volunteers. Blood samples were collected over 24 hours for serum paracetamol, glucuronide and sulphate metabolite concentration estimation. The following parameters were compared: maximal concentration (C_{max}), area under the curve (AUC), time to C_{max} (T_{max}) and elimination half-life (t_{1/2}).

Results:

As with the previous study, PEX exhibited significantly lower paracetamol C_{max} (252.33µmol/L vs. 565.56µmol/L P= 0.0421), AUC (1992.0µmol/h/L vs. 2574.7µmol/h/L p = 0.0221) and delayed T_{max} (2.889hrs vs. 1.389 hrs P = 0.0189) than APAP-IR. Comparison of sulfate metabolite PK parameters for both preparations, PEX vs APAP-IR, showed similar AUC (1049.2µmol/h/L vs. 960.0µmol/h/L), T_{max} (3.889hrs vs. 4.444hrs), C_{max}(95.889µmol/L vs 95.889µmol/L) and half-life estimations (3.895hrs vs 3.810hrs). When comparing the glucuronide metabolite concentrations, PEX produced a lower C_{max} (257.44µmol/L vs. 335.22µmol/L, P=0.0239) than APAP-IR, but all other pharmacokinetic parameters were similar, AUC(2537.3µmol/h/L vs. 2813.8µmol/h/L), T_{max} (4.222hrs vs. 3.556hrs) and half-life estimations (3.950hrs vs 3.536hrs).

Conclusions:

There were no major differences between the PK parameters of the two major paracetamol metabolites of these two preparations in simulated overdose. This suggests that the variability in paracetamol AUC seen between the two preparations is most likely explained by concurrent metabolism of paracetamol during the slowed absorption phase seen with PEx.