

Effect of Ibuprofen on the Pharmacokinetics of Paracetamol

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ABSTRACT

The effect of concomitant administration of ibuprofen (1x 400 mg tablet) on the release and absorption of paracetamol (2x 500 mg tablets) was investigated in ten healthy female volunteers in a double-blind crossover study. The Pharmacokinetic parameter values were calculated for paracetamol combined with ibuprofen versus paracetamol alone: AUC_{0-8} 36.60 ± 4.23 vs 33.89 ± 3.11 $\mu\text{g ml}^{-1}\text{hr}$; C_{max} 20.67 ± 2.34 vs 19.55 ± 1.58 $\mu\text{g ml}^{-1}$ and T_{max} 0.5 ± 0.09 vs 0.75 ± 0.07 hr. The extent of paracetamol absorption is slightly greater in the presence of ibuprofen but within bioequivalence limits. The difference in t_{max} values [$p < 0.05$] was statistically significant and therefore it can be concluded that concomitant administration of ibuprofen with paracetamol may result in a more rapid onset of action of paracetamol.

Keywords: Ibuprofen – Paracetamol – Pharmacokinetics – Concomitant.

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INTRODUCTION:

Paracetamol has a weak acidic character, its saturated aqueous solution has a pH of 5.3 to 6.5 at 25°C (National Formulary, 1970). Paracetamol had been reported to be antagonistic to a number of drugs and also reported to show synergism of anti-inflammatory activity with other anti-inflammatory drugs.

Niwa and Nakayama (1968) determined the effect of antipyrine on the plasma level of paracetamol in man. Their results suggested that antipyrine prolonged the peak plasma level of paracetamol. The effect of caffeine on paracetamol absorption was studied (Tukker *et. al.* 1986; Parlik, *et. al.* 1988). No influence of caffeine on the extent of paracetamol absorption but a slight positive influence on the absorption rate was noticed.

It was found that there is no effect of codeine (Faurenes *et. al.*, 1984), aspirin (Muir *et. al.*, 1997) and diazepam (Mulley, 1978) on the bioavailability of paracetamol. It was also found that simultaneous administration of the antacids containing aluminum hydroxide, magnesium hydroxide and dimethicone, slightly delayed paracetamol absorption; however, the antacids did not alter the bioavailability of paracetamol (Anon, 1986). Paracetamol was delayed the absorption of indomethacin (Van *et. al.*, 1985) but increased the uptake of gentamicin and cefotaxime (Hatem *et. al.*, 1999). Recently, the effect of ciprofloxacin on the pharmacokinetics of paracetamol was studied (Issa *et. al.*, 2006). It was found that maximum paracetamol concentration in saliva was significantly decreased when co-administered with ciprofloxacin. It was also found that time to paracetamol concentration was significantly increased in the presence of ciprofloxacin, whereas the area under the concentration-time curve was not affected.

Ibuprofen is a nonsteroidal anti-inflammatory drug of the phenylpropionic acid group. It had been suggested that combination of paracetamol and ibuprofen is advantageous since the additive effects of the individual components increase their efficiency (Kelley, *et. al.*, 1992; Michael *et. al.*, 1993). Studies have demonstrated significant drug interactions between ibuprofen and lithium (Ragheb, 1987) or codeine (Burgos and Moreno, 2002). Other studies failed to find a significant interaction of ibuprofen with cimetidine (Evans *et. al.*, 1989) or zaleplon (Pedro *et. al.*, 2000).

The objective of the study was to investigate whether concomitant administration of ibuprofen has any effect on the release and absorption of paracetamol and any consequent effect on the Pharmacokinetics of paracetamol. In this study, however, clearance estimates were based in part

on salivary measurements of paracetamol concentration, which have been reported to correlate strongly with plasma concentration (Cardot *et. al.*, 1985).

Pharmacokinetic Study:

Ten healthy female volunteers with ages ranging from 20-25 years and weight 65-85 kg, were enrolled in the study. In a randomized two-way crossover design, each subject received on an empty stomach (overnight fasting); either a single one gram dose of paracetamol (two Dexamol tablets, Dexon, B.N. 12603, Exp. 11/06) or both paracetamol (one gram) and ibuprofen (one ibuprofen tablet, 400 mg, Ultrafen, B.N. 040527, Exp. 11/06). Tablets were administered with 200 ml water. No food was allowed for four hours after which a light standard lunch was served. The volunteers were instructed to drink water regularly during the study to maintain saliva flow. Saliva samples (3 ml) were collected before drug administration (blank) and at 0.5, 0.75, 1.0, 1.25, 1.5, 3.0, 6.0 and 8.0 hours. A wash period of 7 days separated each two consecutive phases of the crossover. No other drugs were allowed on the study days and during the wash out period.

To each 1.0 ml standards (5.0, 10.0, 15.0, 20.0 and 25 $\mu\text{g ml}^{-1}$ paracetamol) and to each 1.0 ml saliva samples, 1.0 gram of anhydrous sodium sulfate was added and extracted three times with 5.0 ml portions of ether. The ether layers were collected and evaporated. The residue was dissolved in 1.0 ml of (1:1) HCl and heated on a boiling water bath for 30 minutes; the solution was cooled to room temperature and diluted with 2.0 ml water. 1.0 ml of 1% o-cresol and 2.0 ml of concentrated ammonium hydroxide were added. After 30.0 minutes the absorbance of blue color was measured using uv-visible spectrophotometer (Price *et. al.*, 1983).

The Pharmacokinetic parameters i.e, maximum salivary concentration ($C_{\text{max}} \mu\text{g ml}^{-1}$), time to maximum saliva level (T_{max} , hr.) and area under the saliva level-time curve ($\text{AUC}_{0-8} \mu\text{gml}^{-1}\text{hr.}$) were observed. The area under the saliva level-time curve was calculated using the trapezoidal rule.

Difference between saliva concentration and other parameters when paracetamol was given alone and in combination with ibuprofen were compared using paired t- test. A (p) value < 0.05 was considered to be the level of significane.

RESULTS:

Saliva concentration profiles of paracetamol when administered alone and in combination with ibuprofen were shown in figure 1. Pharmacokinetic parameters of paracetamol are shown in table 1. With regard to the extent of absorption, the AUC_{0-8} takes on values that were slightly greater with the paracetamol plus ibuprofen than with paracetamol alone (mean \pm SD 36.60 ± 4.23 vs $33.89 \pm 3.11 \mu\text{gml}^{-1}\text{hr.}$).

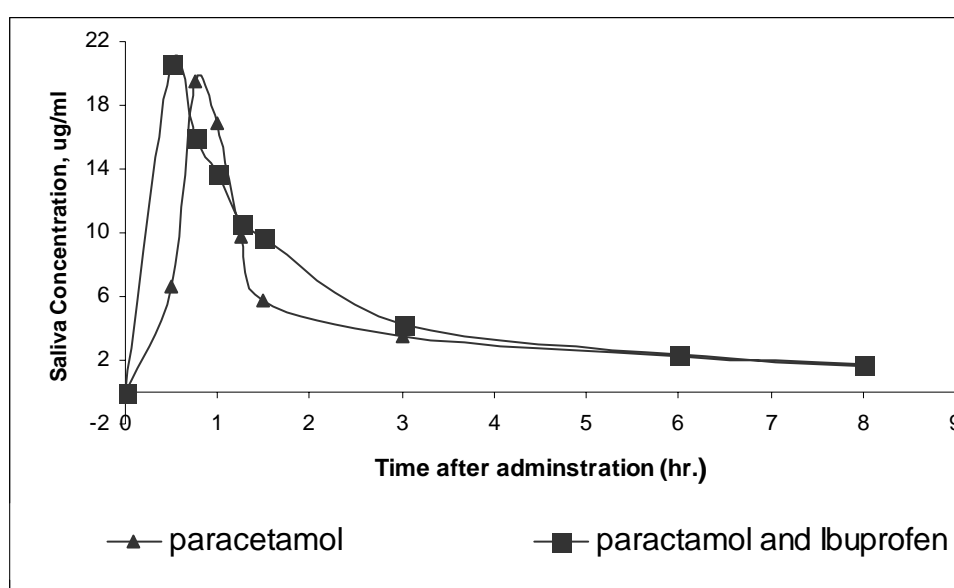


Figure 1. Mean saliva levels of paracetamol (1 gm) given alone and in combination with ciprofloxacin (500 mg) in ten healthy female volunteers.

Table1. Mean (\pm SD) Pharmacokinetic parameters of paracetamol following oral administration of a single 1.0 gram dose, and in combination with ibuprofen (400 mg) in ten healthy female volunteers.

The drug used	C_{\max} (μgml^{-1})	T_{\max} (hr.)	AUC_{0-8} ($\mu\text{gml}^{-1}\text{hr.}$)	C_{\max}/T_{\max}
paracetamol	19.55(\pm 1.58)	0.75(\pm 0.07)	33.89(\pm 3.11)	26.07
paracetamol and ibuprofen	20.67(\pm 2.34)	0.5(\pm 0.09)	36.60(\pm 4.23)	41.34

The results for C_{max} are also slightly different (paracetamol plus ibuprofen versus paracetamol alone: 20.67 ± 2.34 vs $19.55 \pm 1.58 \mu\text{gml}^{-1}$). For the parameter t_{max} , we found some differences (paracetamol plus ibuprofen versus paracetamol alone: 0.5 ± 0.09 vs 0.75 ± 0.07 hr.). In other words the C_{max} for paracetamol occurs 15 minutes earlier with the combination of ibuprofen.

DISCUSSION :

For the concomitant administration of ibuprofen with paracetamol tablets, the quantity of paracetamol absorbed is slightly higher than that of paracetamol alone and is almost within the usual interval of bioequivalence. The maximum concentration is slightly higher for the combination, although it is within the limits of bioequivalence and therefore is considered clinically non-relevant. These data, together with a shorter t_{max} , showed that paracetamol was absorbed from the combination in a quantity equivalent to paracetamol alone at a slight higher rate. We are unable to establish whether the slight differences found were caused by the formulations used or by drug interaction. These findings suggested that the onset of action of paracetamol may be more rapid in patients concurrently receiving ibuprofen.

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