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## Effects of Iron on the Pharmacokinetics of Paracetamol in Saliva

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**Abstract:** Paracetamol has been reported to chelate with iron. It was found that no *in vitro* reaction between ferrous ion and paracetamol. Other studies found that there is an aerobic (in the gastrointestinal tract) oxidation of ferrous ion to ferric ion caused in iron-paracetamol *in vivo* reactions. The objective of this study was to determine if iron interacts with paracetamol and reduces paracetamol absorption. A randomized, double-blind, cross-over study design was used to assess the *in vivo* interaction of paracetamol and ferrous ion. Paracetamol (1.0 g) was co-ingested alone or with (300 mg) ferrous sulphate by ten healthy male volunteers, using saliva drug levels as a parameter. Concomitant administration of ferrous sulphate and paracetamol, decreased AUC<sub>0-8</sub> from 42.88±3.8-34.25±2.8 µg h mL<sup>-1</sup> (p = 0.04) and C<sub>max</sub> from 18.75±1.9 to 15.9±1.7 µg mL<sup>-1</sup> (p = 0.11), while no change in t<sub>max</sub> (p = 0.5) was originated. A significant difference was found in the paracetamol pharmacokinetic parameter oral clearance (Cl/F) (p = 0.02) and slightly increased in volume of distribution (V<sub>d</sub>/F) (p = 0.10). Co-administration of iron and paracetamol results in decreased paracetamol absorption due to an interaction between iron and paracetamol.

**Key words:** Paracetamol, ferrous ion, pharmacokinetic-spectrophotometry

### INTRODUCTION

Iron reduces the absorption of tetracycline (Neuvonen *et al.*, 1970) quinolone, (Kara *et al.*, 1991; Campbell *et al.*, 1992) penicillamine (Osman *et al.*, 1983) mycophenolate (Morii *et al.*, 2000), levodopa (Campbell and Hasinoff, 1989), zinc (Solomons and Jarob, 1981) and captopril (Schaefer *et al.*, 1998). It has been shown that a decrease of mycophenolate mofetil absorption when administered with iron (Morii *et al.*, 2000) and others found no effect of iron on mycophenolate mofetil pharmacokinetics (Lorenz *et al.*, 2004). Paracetamol has been reported to chelate with iron and gives a characteristic violet-blue color (Moffat *et al.*, 2011). Oxidative reactions between paracetamol and iron have been publicized by several studies (Liu and Oka, 1980; Issa *et al.*, 2008). Sunagane *et al.* (2005) found that no *in vitro* reaction between ferrous ion and paracetamol and combined administration of paracetamol and iron showed no influence on bioavailability of paracetamol. However, other studies found that in air, there is no direct reaction between ferrous ion and paracetamol but the aerobic (in the gastrointestinal tract) oxidation of ferrous ion to ferric ion caused in iron-paracetamol *in vivo* reactions (Campbell and Hasinoff, 1989; Campbell *et al.*,

1991). Therefore, the purpose of our study to determine if ferrous ion would alter the pharmacokinetics of paracetamol or not when they administered concurrently.

### MATERIALS AND METHODS

A randomized, double-blind, cross-over study design was used. Paracetamol (1.0 g) co-ingested with either 300 mg ferrous sulfate (inserted in a capsule) or alone by ten healthy male volunteers (average age: 22.1 years, average weight: 76.6 kg, average height 175.6 cm) subsequent to an overnight fast. No food was allowed for 4 h, after which a standard light meal was served. The volunteers were instructed to drink water regularly during the study to maintain saliva flow. A 3.0 mL saliva samples were collected before drug administration as blank and at 0.25, 0.5, 0.75, 1, 2, 4, 6 and 8 h, a washing period of 7 days separated each two consecutive phases of the crossover.

To each 1.0 mL saliva samples, 1.0 g anhydrous sodium sulfate was added and extracted with 5.0 mL portion ether. The ether layers were collected and evaporated. The residues were dissolved in a 1.0 mL of (1:1) HCl and heated on a boiling water bath for 10 min. The solution is subsequently cooled and diluted with

2.0 mL water. Finally 1.0 mL of 1% o-cresol and 2 mL of concentrated ammonium hydroxide were added. After 5.0 min the absorbance was measured using UV-visible spectrophotometer.

Pharmacokinetic parameter values were calculated from the curve of the saliva drug concentrations versus the real time of sampling from each volunteer. The maximum plasma concentration ( $C_{max}$ ) and time to  $C_{max}$  ( $t_{max}$ ) were assigned by visual inspection of the data. The terminal elimination rate constant ( $b$ ) was determined by log-linear regression. The terminal elimination half-life ( $t_{1/2}$ ) was determined by the following Eq. 1:

$$t_{1/2} = \frac{0.693}{b} \quad (1)$$

The area under the paracetamol concentration-time curve up to the last quantified data point was calculated by the linear trapezoidal rule ( $AUC_8$ ) and the  $AUC_{8-\infty}$  was calculated with extrapolation to infinity by dividing the last measured concentration by  $b$ . The sum of these area identified the  $AUC_8$ . Oral clearance was calculated from dose/ $AUC_8$  and reported as  $Cl/F$ . The apparent volume distribution was determined from dose/( $AUC_8 \cdot b$ ) and reported as  $VdF$ .

Ethical approval for the study was acquired from the Palestinian Ministry of Health. All subjects were provided with informed written consent to participate in the study after a detailed explanation of the objectives and nature of the research has been furnished.

Comparison of parameter value between the two groups was completed using the statistics software package (SPSS) and t-test, with significance defined as a p-value <0.05.

## RESULTS

The mean saliva concentration-time curves of paracetamol alone versus the combination paracetamol and iron are shown in Fig. 1. A significant decrease in saliva concentration of paracetamol was noticed at 0.25, 0.75, 1.0, 2.0, 4.0 and 6 h. No significant clinical change was at 0.5 and 8.0 h. Pharmacokinetic parameters of paracetamol are shown in Table 1. The pharmacokinetic parameters of paracetamol (acetaminophen) in ten healthy male volunteers were examined by oral administration of a single 1.0 g dose alone or in combination with ferrous sulfate 300 mg.

With regard to the extent of absorption, concomitant administration of iron decreased the  $AUC_8$  of paracetamol by 20.1% ( $p = 0.04$ ) and  $C_{max}$  by 15.2% ( $p = 0.11$ ). The terminal elimination rate constant ( $b$ ) of paracetamol

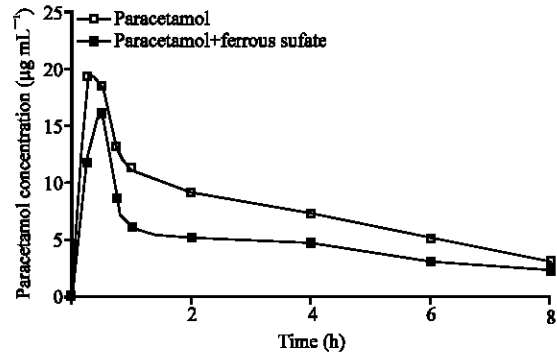


Fig. 1: Mean saliva concentrations versus time of paracetamol 1.0 g given alone or combined with ferrous sulfate 300 mg in ten healthy male volunteers

Table 1: Mean±SD pharmacokinetic parameters of paracetamol (acetaminophen) in ten healthy male volunteers following oral administration of a single 1.0 g dose alone or in combination with ferrous sulfate 300 mg

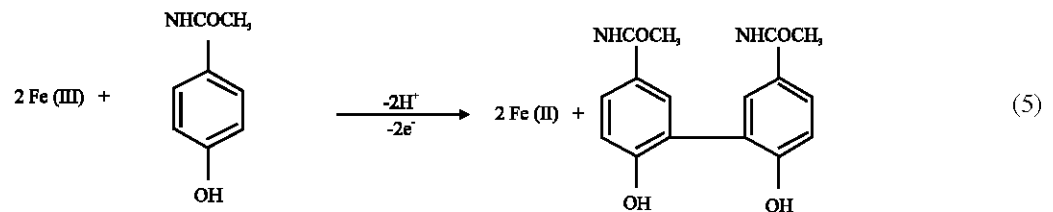
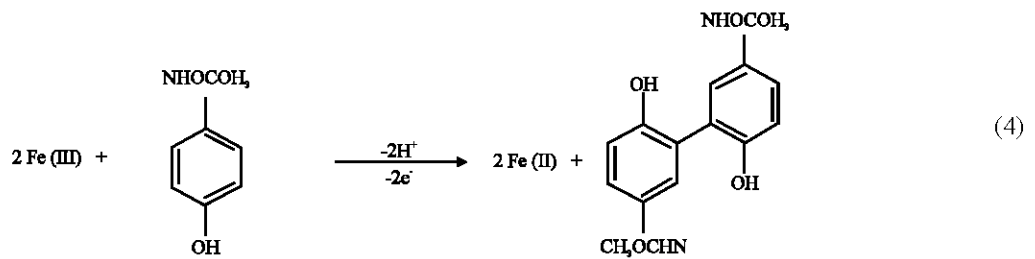
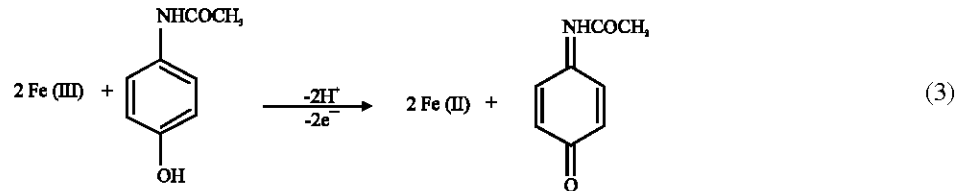
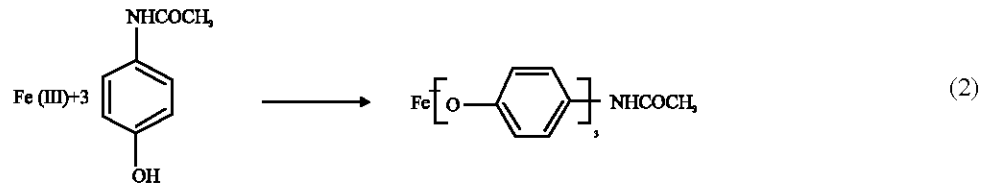
Parameter	Paracetamol	Paracetamol+Iron sulfate	p-value
$C_{max}$ $\mu\text{g mL}^{-1}$	18.75±1.90	15.900±1.70	0.11
$t_{max}$ (h)	0.375	0.375	0.50
$AUC_8$ ( $\mu\text{g} \cdot \text{h mL}^{-1}$ )	36.40±3.30	28.20±2.90	0.04
$AUC_{8-\infty}$ ( $\mu\text{g} \cdot \text{h mL}^{-1}$ )	42.88±3.80	34.25±2.80	0.04
$t_{1/2}$ (h)	1.05±0.12	0.99±0.11	0.15
$b$ ( $\text{h}^{-1}$ )	0.66±0.08	0.70±0.07	0.16
$Cl/F$ ( $\text{L h}^{-1}$ )	388.60±6.30	486.60±6.80	0.02
$Vd/F$ ( $\text{L Kg}^{-1}$ )	0.461±0.023	0.544±0.025	0.10

$AUC_8$ : Area under the concentration-time curve to the time x,  $b$ : Terminal elimination rate constant,  $Cl/F$ : Oral clearance,  $C_{max}$ : Maximum concentration,  $t_{1/2}$ : Half-life,  $t_{max}$ : Time to  $C_{max}$ ,  $Vd/F$ : Apparent volume of distribution

slightly increased by 6.0% ( $p = 0.16$ ). The  $C_{max}$  occurred at approximately the same time.  $Cl/F$  was increased by 25.2% ( $p = 0.02$ ) and  $VdF$  by 18% ( $p = 0.10$ ). Therefore significant differences were found in  $AUC_8$  and  $Cl/f$  when paracetamol administrated with iron.

## DISCUSSION

Concurrent ingestion of ferrous sulfate and paracetamol reduces saliva level of paracetamol. This drug interaction is likely to be clinically significant. Several studies have been reported on the chelation or oxidation of paracetamol. It was chelated with ferric ion and produced a violet blue complexes  $\text{Fe}(\text{paracetamol})_3$  (Moffat *et al.*, 2011). When paracetamol was oxidized, different products like N-acetyl-p-quinoneimine (Issa *et al.*, 2008), Benzoquinone (Issa *et al.*, 2008), 2,2'-dihydroxy-5,5'-diacetylaminobiphenyl (Vilchez *et al.*, 1995) and dimer of paracetamol (Jie *et al.*, 1995) can be formed. The overall reactions in the gastrointestinal tract would thus be.



These reactions would cause a reduction in paracetamol absorption, for example in the chelation reaction (Liu and Oka, 1980) of 300 mg ferrous sulfate, it can stoichiometrically react with approximately 1.0 g of paracetamol in case if all the ferrous transformed to ferric. Figure 1 illustrates that saliva concentrations of paracetamol were decreased significantly after 0.25 (p = 0.011), 0.75 (p = 0.015), 1.0 (p = 0.01), 2.0 (p = 0.011), 4 (p = 0.015) and 6.0 (p = 0.032) h when the drug was concurrently administrated with iron. So it can be believed that a pharmacokinetic drug-drug interaction may have occurred between ferrous ion and paracetamol.

### CONCLUSION

Concomitant administration of iron significantly decreased the extent of absorption of paracetamol and very slightly increased its rate of absorption. These differences may have been caused by a drug-drug interaction. It may be possible to reduce the extent of the interaction by separating the time of ingestion of the two

drugs. In conclusion, care should be taken when prescribing iron preparations with paracetamol to avoid iron-paracetamol interactions.

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