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Pharmacokinetic interaction between grapefruit juice and diclofenac

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Grapefruit juice has been reported to increase the oral availability of many cytochrome P450 substrates, mainly by inhibiting the first-pass metabolism of the drugs metabolized by cytochrome P450 3A in the gut wall rather than in liver. Diclofenac, a nonsteroidal anti-inflammatory drug bearing a carboxilic functional group, undergoes metabolisation by acyl glucuronidation and phenyl hydroxilation, with the latter reaction being catalyzed by cytochrome P450 2C9 and 3A4. This study investigates the pharmacokinetic interaction between diclofenac and grapefruit juice in adult Wistar rats. Mature male Wistar rats weighing 180-200 g were randomized into two groups of 10 animals each. Group I received diclofenac 2.5 mg/kg/day per os for 3 days and to group II was given grapefruit juice 2ml/day for 10 days, followed by a concomitant administration of 2.5 mg diclofenac/kg/day and grapefruit juice 2ml/day for three days. Blood samples were taken at 0,33, 0,66, 1, 2, 3, 6, 8, 12, 24, 36 hours after last drug administration and submitted to the liquid chromatographic analysis of diclofenac in plasma. Statistical analysis was performed using analysis of variance (ANOVA one way) followed by Tukey test. Our results showed that group II presented a statistically significant increased AUC_{tot} (20.206 ± 0.000231 versus 0.0496 ± 0.00017 µg/ml x h, $p<0.05$) and C_{max} (2.23 ± 0.78 versus 0.575 ± 0.22 µg/ml, $p<0.05$) compared to group I. Diclofenac serum levels at 0.33, 0.66 and 1 hour after drug last administration in group II were statistically significant elevated compared to group I (2.23 ± 0.3 versus 1.12 ± 0.02 µg/ml, 1.34 ± 0.2 versus 0.32 ± 0.01 µg/ml and 1.22 ± 0.22 versus 0.55 ± 0.03 µg/ml, $p<0.05$). The present study demonstrates that grapefruit juice significantly influences the pharmacokinetics of diclofenac.