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Notes

Effect of metoclopramide on ketoprofen pharmacokinetics in man

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Summary

The effect of oral administration of metoclopramide (10 mg) on the absorption of ketoprofen from a capsule dosage form (50 mg) was studied in four healthy subjects in a cross-over design. The plasma concentrations of ketoprofen were determined by a HPLC technique The results demonstrated a marked decrease in drug levels during coadministration with metoclopramide in the first 2 h post-dose Metoclopramide resulted in markedly lower AUC and C_{max} values with a longer T_{max} of ketoprofen in comparison with the corresponding values for the drug alone The results suggest that the gastric phase of ketoprofen absorption is the determinant step of the process Rapid transit of the capsule, due to metoclopramide, reduces the time required for adequate dissolution and absorption.

Ketoprofen belongs to the category of acidic nonsteroidal anti-inflammatory drugs (NSAIDs); it is widely used as an analgesic and antirheumatic. This group of drugs is known to produce hyperacidity, gastric upset and in some cases gastric lesions. Concomitant administration of ketoprofen and drugs intended to reduce its gastrointestinal side effects is probably necessary. Interactions of ketoprofen and many of these relieving agents have been reported (e.g., Eshra et al., 1988).

Drugs accelerating gastric emptying rate, such as metoclopramide, are used to overcome the gastric side effects associated with, for example, cancer therapy and following surgery (Reynolds and Prasad, 1982). A change in gastric emptying may have a pronounced effect on the onset of action, the overall rate of drug absorption, the intensity of the effect and the biological availability. Rapid gastric emptying improves the absorption of basic drugs, since they rapidly reach the proper site of absorption; the intestine. The expected effect of metoclopramide on acidic drugs is a decrease in drug absorption, since such drugs travel rapidly through the main site of absorption; the stomach. However, an improvement in aspirin absorption has been reported for drug interaction when metoclopramide was taken by migrainous patients 3 min earlier (Miners, 1989).

Since the effect of metoclopramide on acidic

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drugs is unpredictable, in contrast to that on basic drugs, evaluation of the combination of metoclopramide and acidic drugs is important. The present study reports the effect of metoclopramide on the pharmacokinetics of ketoprofen.

Four healthy male volunteers participated in this study after giving their signed consent. They fasted overnight before drug administration and continued for 4 h post-dose. One 'Primperan' tablet (10 mg metoclopramide), and one 'Profenid' capsule (50 mg ketoprofen), were given to each volunteer. The drugs were swallowed at 8 a.m. with 200 ml of water. Venous samples (2 ml) were collected in heparinized vacutainer tubes. Ketoprofen plasma concentrations were determined by a HPLC method (Abd-Elhamid and Etman, 1990). Chromatographic separations were performed on a 10 μm reversed phase RP-8 Perkin Elmer column 4.6 × 250 mm. The mobile phase consisted of acetonitrile : water (1 : 1 v/v) adjusted to pH 4.0. Peak heights of ketoprofen and diclofenac (internal standard) were measured and peak height ratios were calculated. The concentration of ketoprofen in each sample was evaluated from peak height ratios of standards to their concentrations. Mean plasma ketoprofen concentrations were fitted to a stripping computer program to calculate the area under the plasma concentration-time curve and other pharmacokinetic parameters.

The plasma concentrations of ketoprofen following ketoprofen administration either alone, as determined previously (Abdel-Hamid et al., 1990), or in combination with metoclopramide tablets are illustrated in Fig. 1. The results indicate a clear difference in plasma levels between the two regimens. The decrease in ketoprofen concentration due to coadministration with metoclopramide is more distinct during the first 2 h post-dose, reaching a maximum after 1.5 h (about 50% reduction). Subsequently, the difference in plasma levels declined to minimal value after 3 h. The different pharmacokinetic parameters were further evaluated, the data being listed in Table 1. It is clear from the above results that metoclopramide induced appreciable reduction in the AUC(0–8 h) and AUC(0–∞) ranging to about 30%. It is also clearly evident, from the results in

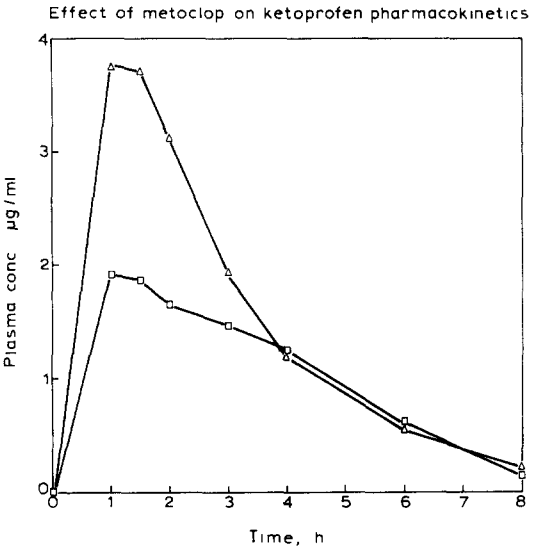

Fig. 1. Mean plasma concentration-time curves following administration of 50 mg ketoprofen capsule (△ ——— △) alone and in combination with 10 mg metoclopramide tablet (□ ——— □)

Table 1, that metoclopramide caused a marked decrease in the maximum plasma ketoprofen concentration (C_{max}) from 3.76 to 1.97 μg/ml. In addition, the time to reach this maximum (T_{max}) was also lengthened from 1.04 to 1.38 h after coadministration of the drug with metoclopramide. The above findings demonstrate that metoclopramide resulted in appreciable decreases in the rate and extent of ketoprofen absorption, which could lead to subclinical levels of the drug.

TABLE 1

Mean pharmacokinetic parameters following administration of 50 mg ketoprofen capsule alone and in combination with 10 mg metoclopramide tablet

Parameter	Ketoprofen	Ketoprofen + metoclopramide
AUC (0–8 h)	12 08	8.71
AUC (0–∞)	12.58	9.07
C_{max} (μg/ml)	3 76	1.97
T_{max} (h)	1 04	1 38
$t_{1/2}$ (h)		
Absorption	0 33	0.50
Elimination	1.59	1.81

Since the majority of drug substances are classified as weak organic acids or bases, the pK_a and pH of the medium at absorption site affect the ratio of the undissociated form of the drug, and hence its absorption. Accordingly, ketoprofen which is a propionic acid derivative (pK_a 4.5) would be mostly in the unionized form in the acid medium of the stomach. This could explain the observed reduction in bioavailability and C_{max} and the prolonged T_{max} of ketoprofen when given concomitantly with metoclopramide (Table 1 and Fig. 1).

The most dramatic effect of metoclopramide was observed during the first 2 h post-dose (Fig. 1), which represents the time of action of metoclopramide on the gastric emptying rate. This observation leads to the suggestion that, the gastric phase of absorption of ketoprofen appears to be the dominant phase and that the stomach is the main site of its absorption. Furthermore, Manninen et al. (1973) reported that metoclopramide decreased the amount of digoxin absorbed from tablets, but not when digoxin was given in solution form. Alternatively, the same authors observed that propantheline increased the amount absorbed from digoxin tablets, which was due to the increase in the effective time available for dissolution of the drug.

It could be concluded that drugs increasing gastrointestinal motility, such as metoclopramide, reduce the bioavailability of sparingly soluble drugs, if given in solid dosage forms. This is primarily due to the decrease in time available for dissolution of the drug in the stomach. Our suggestions are supported by the observed greater bioavailability reported for poorly soluble drugs when coadministrated with propantheline, e.g., digoxin (Manninen et al., 1973), hydrochlorothiazide (Beerman and Groschinsky-Grind, 1978) and nitrofurantoin (Jaffe, 1975). Propantheline increases the residence time of the drug in the stomach and hence leads to a greater extent of drug dissolution.

In conclusion, it is recommended that metoclopramide and similar drugs, inducing rapid gastric emptying, should be administered, where necessary, 1–2 h after administration of ketoprofen and possibly other acidic non-steroidal anti-inflammatory drugs.

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