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Influence of caffeine on the renal effects and solubility of ketoprofen

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Summary

The effect of administration of ketoprofen capsules with water or tea on urine output was studied in healthy subjects. Statistical analysis of the results indicated significant reduction of urine volume, yet the decrease in the case of tea was higher than that with water. This finding was explained on the basis of physical and pharmacological interactions between ketoprofen and caffeine. The reduction of urine volume was explained by interference of both ketoprofen and caffeine with the renal prostaglandins. Further, the solubility of ketoprofen appeared to increase linearly with the concentration of caffeine employed, suggesting the formation of 1 : 1 complex. It could be concluded that during administration of ketoprofen and possibly similar drugs: (a) drinking of caffeine-containing beverages should be avoided, (b) drugs tending to precipitate in the urinary tract, e.g. sulphonamides, must be prescribed with caution, (c) kidney function tests should be performed regularly if such drugs have to be used over long periods.

Ketoprofen belongs to the widely employed non-steroidal anti-inflammatory drugs (NSAIDs). Some personal observations and published data (e.g. Yeung-Laiwah and Mactier, 1981) described reduced urine output, hypertension, oedema and elevation of blood urea and creatinine levels during therapy with these drugs. Accordingly, administration of NSAIDs, especially during long-term therapy, could substantially increase the tendency of crystaluria involving both natural metabolites or coadministered relatively insoluble drugs which are mainly excreted in the urine, e.g. sulphonamides. Therefore, the present work was undertaken in an attempt to counteract the fluid-retaining properties of NSAIDs, exemplified by ketoprofen, by taking the dosage forms with a cup of tea. Further, the possible in vitro interaction of ketoprofen and caffeine was assessed by the solubility method.

Four healthy human males between 28 and 40 years old, weighing 60–90 kg and capable of informed consent, participated in this study. Each subject swallowed in the morning, after an overnight fasting, one 'Profenid' capsule (50 mg ketoprofen) with 200 ml of either water (regimen A) or tea (regimen B). Control experiments for both

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TABLE 1

Individual and cumulative urine volumes (ml) after administration of 50 mg ketoprofen capsules with either water (regimen A) or tea (regimen B)

Subject	Regimen A					Regimen B				
	1 h	2 h	3 h	4 h	0–4 h	1 h	2 h	3 h	4 h	0–4 h
AN	25	12	30	120	187	22	20	16	12	70
	(58)	(50)	(60)	(80)	(248)	(56)	(150)	(200)	(140)	(546)
ME	20	15	22	88	145	18	21	18	23	80
	(49)	(47)	(53)	(66)	(215)	(51)	(93)	(112)	(117)	(373)
YS	18	22	35	22	97	22	28	35	22	107
	(30)	(40)	(68)	(40)	(178)	(39)	(60)	(75)	(80)	(245)
AE	21	16	29	76	142	21	23	23	15	82
	(45)	(45)	(60)	(62)	(212)	(48)	(109)	(132)	(112)	(401)
Mean	21	16.25	29	76.5	142.8	20.75	23	23	18	84.75
	(45.5)	(45.5)	(60.3)	(62)	(213.3)	(48.5)	(103)	(129.8)	(112.3)	(393.5)
SD	2. 9	4.2	5.4	40.8	36.8	1.9	3.6	8.5	5.4	15.7
	(11.7)	(4.2)	(6.1)	(16.6)	(28.6)	(7.1)	(37.4)	(52.4)	(24.7)	(120)
t value	5.38	6.98	49.68	−1.2	12.45	7.11	3.96	3.59	6.58	4.58

Values in parentheses are the control values. SD, standard deviation of the sample mean. *t* value: paired Student's *t*-test between the mean experimental values and their respective control values.

regimens were carried out for each volunteer, omitting the administration of the drug. Each subject evacuated the bladder just before starting the experiments and was requested to drink 200 ml of water per h. No medication was taken during and at least 1 week before the study. Treatments were separated by about 1 week. The cumulative urine volume (0–4 h), the volume per h and the corresponding values for the controls are presented in Table 1. The statistical analysis of these results by the two-way analysis of variance (ANOVA-2) indicated significant difference between the two regimens and insignificant difference between subjects at $P = 0.05$. Moreover, the mean urine volumes of the experimental and the respective control values were statistically different as compared by the paired Student's *t*-test. It is obvious from the above results that administration of ketoprofen with water resulted in significant reduction of urine volumes. Subsequently, it could be expected that the urine concentration associated with administration of NSAIDs would result in the precipitation of many natural metabolites or drugs in the urinary tract. The reduction of urine output could be explained by inhibition of PG synthesis induced by ketoprofen, resulting in a decrease in the total renal blood flow, as well as in the inner and outer cortical medullary blood flow (Del Favero, 1981). In addition, the inhibition of PG synthesis enhances the renal vasoconstrictor action of angiotensin-II and norepinephrine and abolishes renal blood flow autoregulation (Mauk et al., 1977). Therefore, in an attempt to restore normal urine output, the ketoprofen capsule was swallowed with 200 ml tea (regimen B) to take advantage of its diuretic effect, since the observed mean cumulative control urine volume with tea was almost double that with water. However, the results obtained after administration of the drug (regimen B) indicated much more urine reduction in comparison with water (regimen A) (Fig. 1 and Table 1). The observed mean decrease in cumulative urine volume, in relation to the control, was 33 and 78% for regimen A and B, respectively. The failure of tea to increase the urine output, or even to maintain the volumes encountered with water (regimen A) might be explained by pharmacological and/or physical interactions as follows. First, Cooper and Malik (1985) pointed out the negative effect of caffeine on PG synthesis stimulated by some vasoactive substances such as norepinephrine and angioten-

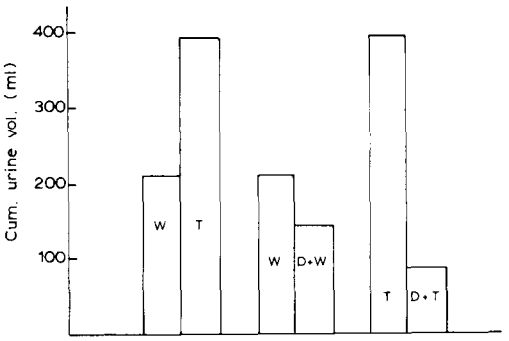

Fig. 1. Cumulative urine volume (0–4 h) following the oral administration of 50 mg ketoprofen capsule with water or tea and the corresponding control values. W, water; T, tea; K, ketoprofen.

sin II. Second, caffeine is well known to form complexes with many drugs (e.g. Higuchi and Lach, 1954). Therefore, the effect of increasing caffeine concentration on the solubility of ketoprofen, which is practically insoluble in water, is illustrated in Fig. 2. The results obtained show a linear relationship ($r = 0.981$). This finding suggests complex formation, having more likely a 1 : 1 ratio. The observed increase in ketoprofen solubility in the presence of caffeine would result in higher dissolution from the capsules, better bioavailability and higher concentrations in the kidney. Consequently, more inhibition of PG synthesis and hence greater reduction in renal blood flow and urine output would be encountered (regimen B).

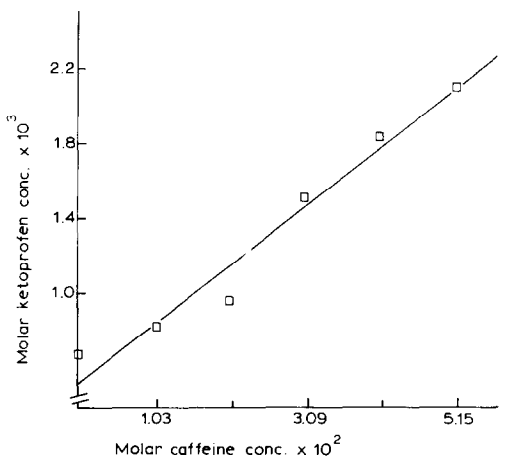

Fig. 2. Effect of molar caffeine concentration on the molar solubility of ketoprofen in water at 37 °C. ($y = 0.00053 + 0.0305x$, $r = 0.981$)

In conclusion, the results of this study indicate that: (a) administration of caffeine-containing beverages should be restricted during therapy with ketoprofen and related drugs; (b) administration of ketoprofen and possibly other NSAIDs should be cautiously prescribed to patients most likely to be affected by fluid retention, e.g., in the case of cardiac failure, liver cirrhosis, hypertension, etc.; (c) patients on NSAID therapy and coadminister some drugs likely to precipitate in the urinary tract, for example sulphonamides, would be at higher risk of crystaluria; and (d) prolonged use of NSAIDs should be accompanied by regular kidney function tests.

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