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Therapeutic Doses of Codeine Have no Effect on Acetaminophen Clearance or Metabolism

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Summary. In nine healthy volunteers, the clearance and metabolism of acetaminophen 1000 mg i.v. was evaluated with and without two concomitant oral doses of codeine in order to investigate a possible interaction. Plasma acetaminophen was followed for 720 min and urine was collected for 24 h after each dose for determination of metabolites.

When codeine was coadministered, the average total clearance of acetaminophen and its clearance by glucuronidation, sulphation and mercapturate formation were 0.58 to 1.12-times the control values.

It is concluded that therapeutic doses of codeine do not influence the clearance or metabolism of acetaminophen.

Key words: acetaminophen, codeine; clearance, metabolite formation, glucuronidation, pharmacokinetics, healthy volunteers, drug interaction

A combination of acetaminophen (paracetamol) and codeine has been suggested for the treatment of mild to moderate pain [1, 2]. Both drugs have moderate analgesic potency and exert their effects through peripheral and central actions, respectively. In man the elimination both of acetaminophen and codeine is mainly dependent on glucuronide conjugation [3, 4]. Sharing the same metabolic pathway, codeine might theoretically inhibit the glucuronidation of acetaminophen, leading to a shift to oxidative pathways of acetaminophen metabolism. The result could be greater formation of a reactive intermediate, which is inactivated by glutathione conjugation. In man the capacity for conjugation with glutathione is thought to be limited and, if exceeded, the intermediate might accumulate. As the reactive metabolite is believed to initiate liver damage in cases of acetaminophen overdose, there is a clear possible toxicological consequence of an interaction between the glucuronidation of acetaminophen and codeine.

In the present study the effect of a single therapeutic dose of codeine on the clearance and metabolism of acetaminophen in healthy human volunteers was investigated.

Materials and Methods

Ten healthy volunteers, 4 females and 6 males, gave their informed consent to participation in the study. The protocol was approved by the local ethical committee. They took no drugs for 2 weeks prior to the study. Routine laboratory tests were normal in all the subjects except one, who had a slightly increased serum bilirubin and serum amylase. She suffered an acute attack of pancreatitis during the codeine-acetaminophen combination and was excluded from the study.

The study was performed on two days separated by 1 week. On both days acetaminophen 1000 mg (500 mg diluted in 50 ml distilled water) was infused i.v. over a period of 5 min. On one of the days, which was chosen at random, the subjects were given codeine 50 mg on the preceding evening at 12 p.m. and again at 7 a.m. after an overnight fast, 1 h before the administration of acetaminophen. After oral administration codeine is characterized by a t_{max} of 1 h and a $t_{½}$ of 2.9 h [5]. From an indwelling cannula in a contralateral forearm vein 10 ml blood samples were collected in heparinized tubes before and 2, 20, 40, 60, 80, 100, 120, 180, 240, 300, 360, 420, 600 and 720 min after the acetaminophen dose. Plasma was separated and stored at −20 °C until

Table 1. Clinical and pharmacokinetic data in 9 subjects after acetaminophen (APAP) 1000 mg i. v. without (1) and with (2) concomitant doses of codeine 50 mg

Subject	Sex (F/M)	Age (years)	Weight (kg)	Smoker (+/−)	CL^1_{APAP}[a] ($ml \cdot min^{-1}$)	CL^2_{APAP} ($ml \cdot min^{-1}$)	V^1 (l)	V^2 (l)	$t^1_{½}$ (min)	$t^2_{½}$ (min)	CL^1_R ($ml \cdot min^{-1}$)	CL^2_R ($ml \cdot min^{-1}$)	Rec^1 (%)	Rec^2 (%)
1	M	33	65	−	393,1	328,0	79,9	59,7	144	127	25,6	26,7	96	99
2	F	29	54	+	249,1	226,7	57,0	67,2	177	281	27,9	29,8	86	84
3	F	33	55	+	312,1	307,1	47,5	48,7	112	116	23,6	28,3	100	124
4	M	39	67	−	299,0	267,0	79,1	64,8	205	177	16,7	17,2	94	110
5	M	34	70	−	325,2	320,9	60,9	63,2	136	142	43,3	32,0	101	93
6	M	30	65	−	257,3	276,2	30,9	64,8	191	177	8,2	15,6	57	97
7	M	29	65	−	252,9	227,3	58,4	56,6	166	183	29,4	34,8	97	106
8	F	29	56	−	251,8	315,6	63,2	52,6	188	116	24,4	13,7	52	89
9	M	39	87	−	349,7	330,4	124,8	99,8	274	263	54,4	43,9	126	124
Mean					298,9	288,8	66,9	64,2	177,0	175,7	28,2	26,9	90	103

[a] APAP: N-acetyl-p-aminophenol

analysis. Urine was collected for 24 h after drug administration for determination of parent drug and metabolites. Plasma acetaminophen was determined by HPLC [6]. Metabolites and acetaminophen in urine were determined by a modification of the method of Moldeus [7, 8]. The cysteine conjugate could not be determined due to interfering endogenous peaks. Pharmacokinetic calculations were performed by means of the ESTRIP program [9]. Clearance in each elimination pathway was estimated as the amount of parent compound or metabolite excreted in terms of acetaminophen equivalents divided by the area under the plasma concentration of acetaminophen vs time curve during urine collection.

Student's t-test for paired data was used for statistical analysis; $p < 0.05$ was chosen as the level of significance.

Results

The clinical and pharmacokinetic data of acetaminophen in 9 subjects are listed in Table 1. Coadministration of codeine did not significantly change the elimination half-life or the clearance of acetaminophen from plasma ($p > 0.05$; paired t-test), nor was the renal clearance of parent drug or the recovery affected. Clearance via production of the glucuronide (CL_{Glu}), sulphate (CL_{Sul}) and mercapturate (CL_{Mer}) metabolites is shown in Table 2. None of those metabolic pathways was influenced by concomitant administration of codeine. The ratios between the clearance values obtained during administration of acetaminophen and those from the coadministration of codeine were 1.04 (0.95 to 1.13; mean and 95% confidence intervals) for the total clearance of parent compound, 0.89 (0.68 to 1.10) for partial clearance by glucuronidation, 0.90 (0.74 to 1.16) by sulphation and 1.72 (0.03 to 3.41) by mercapturate formation.

Table 2. Clearance (CL) for production of the major metabolites of acetaminophen without (1) and with (2) concomitant codeine

Subject	CL_{Glu}*		CL_{Sul}*		CL_{Mer}*	
	1	2	1	2	1	2
1	226,4	182,9	112,3	131,3	12,5	13,7
2	112,2	101,4	66,3	50,5	7,2	18,1
3	193,4	274,4	83,5	97,2	10,9	9,0
4	164,1	172,3	82,3	100,0	17,2	18,5
5	161,2	158,1	111,6	99,3	13,8	11,8
6	99,6	190,8	28,0	49,0	11,3	7,8
7	113,5	118,5	87,9	92,5	13,8	7,7
8	66,2	177,0	37,7	60,1	2,7	9,1
9	258,0	264,2	89,3	104,7	39,1	5,3
Mean	155,0	179,2	77,7	87,2	14,3	11,2

* ($ml \cdot min^{-1}$)

Discussion

The results show that a single therapeutic dose of codeine does not change the pharmacokinetics of intravenous acetaminophen, and especially it does not change the clearance of acetaminophen to its glucuronide metabolite. In man mutual inhibition at the level of glucuronidation has been demonstrated for both salicylic acid and salicylamide, and acetaminophen and salicylamide [10]. In animal studies oxazepam, morphine, dicoumarol and chloramphenicol have been shown to inhibit formation of the glucuronide of acetaminophen [11, 12]. A single dose of phenobarbital in mice has been shown to enhance the hepatotoxicity of acetaminophen [13]. The second step of the metabolism of pheno-

barbital involves conjugation with glucuronic acid, and it may be where an interference with the glucuronidation of acetaminophen occurs.

Induction of glucuronyltransferases has been demonstrated in several animal and human studies of well known inducers of drug metabolism, and multiple isozymes of the UDP-glucuronyltransferases have been characterised [14, 15]. This functional heterogeneity may also explain why the glucuronide conjugation of acetaminophen was not impaired here. In humans it has recently been suggested that acetaminophen glucuronidation is susceptible both to phenobarbital- and 3-methylcholanthrenetype inducers [16]. As proposed, two or more different isozymes may catalyze the glucuronidation of acetaminophen and this would add to the difficulty of interpreting interaction studies. If, on the other, the two drugs were to share the same enzyme, codeine might have a much higher affinity than acetaminophen if inhibition were demonstrated, since the molar amount of acetaminophen was several times larger than that of codeine. Clinically, the administration of single doses of acetaminophen and codeine in combination can be considered safe from a toxicological point of view. However the results cannot be extrapolated to a large overdose of either or both drugs, or chronic dosing with the combination.

It is concluded that single therapeutic doses of codeine do not affect the clearance or metabolism of acetaminophen.

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