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# Influence of the CYP2D6 polymorphism and hemodialysis on codeine disposition in patients with end-stage renal disease

Hadi Molanaei · Juan Jesus Carrero · Olof Heimbürger · Louise Nordfors · Bengt Lindholm · Peter Stenvinkel · Ingegerd Odar-Cederlöf · Leif Bertilsson

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## Abstract

**Objective** We studied the influence of three factors on drug disposition: genetic polymorphism, impaired renal excretion of drug metabolites, and the possible elimination by hemodialysis (HD), using codeine as a model drug.

**Methods** Based on the genotyping of three CYP2D6 polymorphisms in 228 HD patients, nine extensive metabolizers (EMs) and two poor metabolizers (PMs) were given a single oral dose of 50 mg codeine phosphate. Plasma concentrations of its metabolites codeine-6-glucuronide (C6G), morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) were determined after 2, 4, 6, 8 and

24 h (beginning of the HD session) and again after 4 h of HD (28 h). Codeine metabolites in plasma were quantitated by liquid chromatography–mass spectrometry (LC–MS).

**Results** The concentrations of C6G in plasma were high and similar in EMs and PMs. Two hours after the codeine intake, the mean concentration of M3G was 210 nM in EMs vs. 3.5 nM in PMs. The M6G metabolite concentrations could be quantitated in EMs but were below the limit of quantification in PMs (<1 nM). All three codeine metabolites/glucuronides remained unchanged or even increased until the start of HD, and thereafter, the concentrations decreased dramatically during the HD procedure.

**Conclusions** Formation of the codeine metabolites M3G and M6G was dependent on the CYP2D6 genotype, as previously shown in healthy individuals. Elimination of glucuronides in these patients was absent until HD was performed. These factors need to be taken into consideration when drugs metabolized by CYPs are prescribed in HD patients.

H. Molanaei · J. J. Carrero · O. Heimbürger · B. Lindholm · P. Stenvinkel  
Divisions of Renal Medicine and Baxter Novum,  
Department of Clinical Science, Intervention and Technology,  
Karolinska Institutet,  
Stockholm, Sweden

L. Nordfors  
Neurogenetics Unit, Department of Molecular  
Medicine and Surgery, Karolinska Institutet,  
Stockholm, Sweden

I. Odar-Cederlöf · L. Bertilsson  
Division of Clinical Pharmacology, Department of Laboratory  
Medicine of Karolinska Institutet, Karolinska University Hospital,  
Huddinge,  
141 86 Stockholm, Sweden

H. Molanaei (✉)  
Division of Renal Medicine, Karolinska University Hospital,  
Huddinge,  
141 86 Stockholm, Sweden  
e-mail: hadi.molanaei@karolinska.se

**Keywords** Codeine metabolism · CYP2D6 polymorphism · Hemodialysis

## Introduction

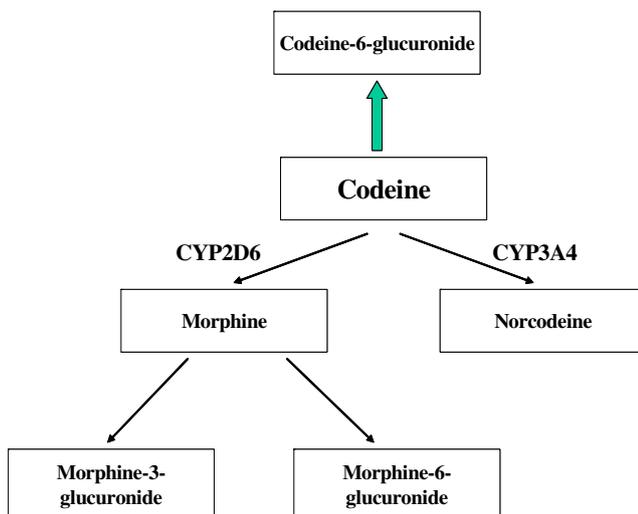
Analgesic treatment of hemodialysis (HD) patients offers challenges to nephrologists. Codeine is widely used, often in combination with other analgesics, such as paracetamol. However, there is limited information on the pharmacokinetics of codeine in patients with end-stage renal disease (ESRD) treated with HD. Codeine can be used as a model drug to study both the influence of the genetically determined

metabolism of drugs as well as the influence of renal failure and HD on elimination of the drug and its metabolites.

Codeine is metabolized by the polymorphic cytochrome P450 2D6 (CYP2D6) enzyme [1, 2]. The prevalence of poor (PM) and extensive (EM) metabolizers varies among different populations. Four major mutant alleles termed CYP2D6\*3–\*6 are associated with the PM genotype/phenotype in Caucasians. The CYP2D6\*4 allele has a frequency of 22% in Swedish Caucasians and accounts for >75% of the detrimental alleles in this population [3]. As this allele is almost absent in Chinese, the prevalence of PMs is low: 1% compared with 6% in Caucasians [4]. The alleles CYP2D6\*1 and \*2 comprise the EM phenotype, and its duplication/multiplication leads to higher metabolic activity. Gene duplication shows a European African, north–south gradient, with a prevalence of 1–2% in Swedish Caucasians and 29% in Ethiopians [5]. The polymorphisms are named according to The Cytochrome P450 (CYP) Allele Nomenclature Committee (<http://www.cypalleles.ki.se>).

Codeine has many known metabolites, e.g., morphine (M), morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G), nor-codeine (NC), and codeine-6-glucuronide (C6G). The major metabolite is C6G, representing about 70% of codeine metabolism (Fig. 1). Codeine is also O-demethylated by CYP2D6 to M and via N-demethylation by CYP3A isoenzymes to NC. Morphine is glucuronidated to M6G, which has a stronger analgesic effect than morphine itself [6]. As codeine exerts its analgesic effect via morphine and M6G, the drug is ineffective in PM [7] due to the inability to metabolize codeine to its active metabolites.

In this study we investigated the pharmacokinetics of codeine metabolites in patients with ESRD treated with HD characterized according to CYP2D6 genotypes.



**Fig. 1** Major pathways of codeine metabolism

## Material and methods

### Patients

This study was performed at the Karolinska University Hospital, Huddinge, Sweden, and its satellite HD units in the Stockholm area. Patients who agreed to participate in our study gave their written informed consents on the basis of verbal and written information. The Ethics Committee of the Karolinska Institutet approved the study. Initially, 228 prevalent adult HD patients were genotyped regarding CYP2D6. Thirteen patients (5.7%) had two variant alleles representative of PMs. The remaining patients were considered as EMs. A selected group of the patients was able to participate in a subsequent pharmacokinetic study (two PMs and nine EMs). The general characteristics of the 11 patients participating in this pharmacokinetic study are presented in Table 1.

### Methods

#### *CYP2D6 genotyping by pyrosequencing*

For analysis of the CYP2D6\*3, \*4, and \*6 alleles (rs35742686, rs3892097 and rs5030655, respectively), primers were as reported by Zackrisson and Lindblom [8]. All oligonucleotides were synthesized by Thermo Electron Corporation (Waltham, MA, USA). The pyrosequencing

**Table 1** General characteristics of the nine extensive (EMs) and two poor (PMs) metabolizers included in the study

	EM (n=9)	PM 1	PM 2
Age (years)	66 (47–76)	77	55
Female/male (n)	3/6	Male	Male
Time on dialysis (months)	57±6	60	12
BMI (kg/m <sup>2</sup> )	26±4	32	30
Albumin (g/l)	36±4	39	40
Kt/v	1.45±0.19	1.35	1.44
Urea reduction rate (%)	75±0.1	66	56
Diabetes mellitus (n)	2	Yes	Yes
Cardiovascular disease (n)	3	Yes	Yes
Primary kidney disease	DM 2 GN 4 Vasculitis 1 Unknown 2	DM	PCKD

Data are expressed as mean ± standard deviation (SD) or median (range), unless otherwise noted

*BMI* body mass index, *DM* diabetes mellitus, *GN* chronic glomerulonephritis, *PCKD* polycystic kidney disease. *Kt/V* index number used to measure the adequacy of hemodialysis treatment (K = dialyzer's clearance of urea, t = dialysis time, and V = volume of distribution for urea = total body water)

reaction was performed on a PSQ96<sup>TM</sup>MA instrument from Biotage AB (Uppsala, Sweden), as described previously [9].

### Codeine administration and analysis of metabolites in plasma

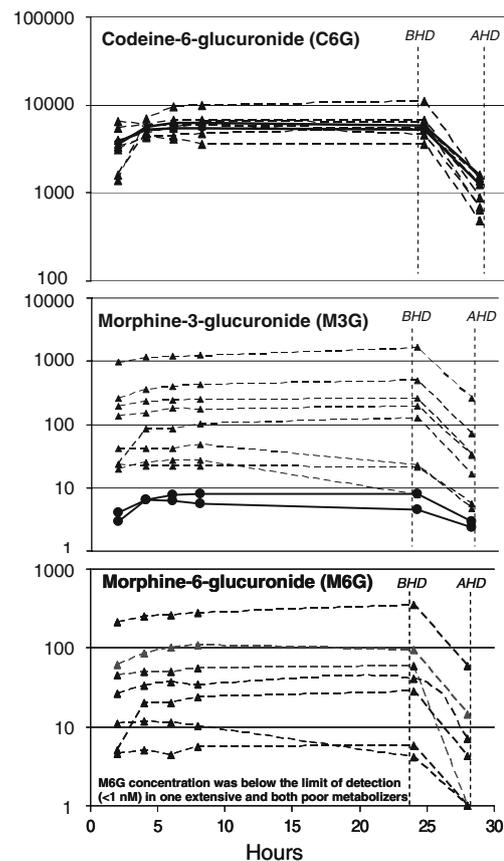
Patients were given a single oral dose of 50 mg codeine phosphate (Kodein Recip<sup>®</sup> 2 x 25 mg) at 8 A. M. following an overnight fast. Blood samples (10 ml) were drawn via an indwelling intravenous catheter into heparinized Vacutainer<sup>®</sup> tubes before codeine intake and after 2, 4, 6, 8, and 24 (concurrent with the beginning of the hemodialysis session), and 28 h (concurrent with the end of the 4-h hemodialysis session). Samples were centrifuged and plasma separated and stored frozen at  $-20^{\circ}\text{C}$  until analysis. Codeine metabolites C6G, M3G, and M6G were quantitated by liquid chromatography–mass spectrometry (LC–MS) with atmospheric pressure ionization–electrospray (API-ES) detection, as described by Svensson et al. [10]. The lower limit of quantification for these three substances was 1 nM. The coefficient of variation (within and between days) of concentrations of C6G, M3G, and M6G was <15%. Unconjugated codeine and morphine could be quantitated in some but not all patients, and we decided to report only the concentrations of glucuronides, where detailed kinetics could be evaluated.

### Statistical methods

All variables were expressed as mean  $\pm$  SD, unless otherwise indicated. Statistical significance was set at the level of  $p < 0.05$ . Comparisons between two groups were assessed with the nonparametric two-tailed Wilcoxon signed-rank test for matched pairs. All statistical analyses were performed using JMP software (SAS Institute Inc) version 7.0.1.

### Results

Thirteen out of the 228 patients (5.7%) were genotypically PMs on the basis of their CYP2D6\*3, \*4, and \*6 alleles. Eleven patients completed the pharmacokinetic study with codeine. Of those, two PMs had the CYP2D6\*4/\*4 genotype, four EMs had the CYP2D6\*1/\*4 genotype, and five EMs had the CYP2D6\*1/\*1 genotype. Results from one EM patient were not included in the study because of high 0-h concentrations of M3G, M6G, and C6G, indicating that the patient had either taken another codeine-containing drug or taken the test drug earlier than the time indicated in the protocol. Concentrations of C6G were similar in the remaining eight EMs and the two PMs (Fig. 2, Table 2). Plasma concentrations of C6G, M3G, and M6G, which are normally excreted by the kidneys,



**Fig. 2** Plasma concentrations (nM) of codeine-6-glucuronide (C6G), morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in eight extensive metabolizers (EMs) (broken lines) and two poor metabolizers (PMs) (unbroken lines). BHD before hemodialysis, AHD after hemodialysis

increased during the early phase and remained unchanged for 24 h until the start of HD (Fig. 2). Two hours after codeine intake, the mean concentration of M3G was 210 nM in EM compared with 3.5 nM in PM (Fig. 2). M6G was not detectable (<1 nM) in one of the remaining eight EMs and or in either PM. The plasma concentrations of both M3G and M6G were thus much lower in PMs compared with EMs (Table 2), indicating less formation of morphine in PMs. Earlier, larger studies showed a difference in metabolic capacity between CYP2D6 homozygote and heterozygote genotypes [5], but in this small group, there was no significant difference in kinetics. During HD, there was a rapid decrease of plasma concentrations of all three glucuronides, but they could still be quantified in most patients at the end of HD (Table 2).

### Discussion

The frequency of PMs' genotype/phenotype of CYP2D6 in a healthy Swedish population is 6–7% [4], and of 228 HD

**Table 2** Mean plasma concentrations (nM) of codeine metabolites [ $\pm$  standard deviation (SD)] in eight extensive metabolizers (EMs) before and after hemodialysis (HD). Individual values in the two PMs are given; no statistics were calculated, as only two PMs participated

Metabolite	Genotype	Before HD (24h)	After HD (28h)	<i>P</i> value*
C6G	EM	5,591 $\pm$ 2,673	889 $\pm$ 443	0.008
	PM1	5,278	1,266	ND
	PM2	5,851	1,605	ND
M3G	EM	348 $\pm$ 555	53 $\pm$ 86	0.008
	PM1	4.4	2.4	ND
	PM2	8.0	2.9	ND
M6G	EM	74 $\pm$ 118 <sup>a</sup>	11 $\pm$ 20	0.01
	PM1	Not quantifiable (<1 nM)		
	PM2			

C6G, codeine-6-glucuronide, M3G morphine-3-glucuronide, M6G morphine-6-glucuronide, ND not determined

<sup>a</sup> One of the 8 EMs had M6G concentrations <1 nM and is here given the level of 1 nM

\**P* value as assessed by the Wilcoxon signed-rank test for matched pairs

patients studied in our units, 13 (5.7%) were genotypically PMs. Thus, the prevalence of PMs does not differ between Swedish patients with ESRD and healthy Swedish individuals. CYP2D6 gene duplication was not investigated, and it was less likely to find any individual with gene duplication in nine EMs in our study because the frequency of individuals with duplicated/multiduplicated gene in Swedish Caucasians is about 1–2% [11].

Codeine is mainly metabolized by glucuronidation and to a minor extent by CYP2D6 to the active morphine in the liver. Only approximately 3% is excreted unchanged by the kidneys. Plasma half life of codeine is about 3 h in healthy individuals [12, 13]. An earlier study on codeine showed that clearance of codeine metabolites was significantly reduced and the elimination half life of codeine was longer in HD patients compared with healthy individuals, but there was no clinically significant difference in pharmacodynamics [14]. In that study, however, patients were not genotyped, and the impact of hemodialysis on codeine elimination was not studied. In our study, we found that plasma concentrations of glucuronides increased initially and then remained high during the 24 h until HD started (Fig. 2). We showed that M3G and M6G concentrations are markedly lower in PM HD patients compared with EMs. In EMs, the glucuronidated metabolites M3G and M6G reached high plasma concentrations compared with those in normal individuals [12]. This finding is in accordance with earlier studies that showed retention of glucuronidated metabolites of morphine and oxazepam to high concentrations in patients with renal function impairment [14, 15].

In our study, plasma concentrations of glucuronidated metabolites M3G and M6G remained almost unchanged for 24 h after administration of codeine or even tended to increase until the start of the HD session (Fig. 2). Although there was a significant reduction in concentrations of the

three glucuronides by HD, the codeine metabolites were not totally eliminated from plasma. M6G was present in plasma during the interdialytic phase, which may lead to an analgetic effect during this time and possibly the risk of side effects, particularly during treatment with repeated doses when plasma concentrations may increase, as M6G is not completely eliminated by HD (Fig. 2). Plasma concentrations of M3G and M6G were higher in EMs compared with PMs. Also, within the EM genotype group, there was a 100-fold interindividual variation within both metabolites, which is in accordance with earlier studies of codeine and debrisoquine [5]. In HD patients, variability of the CYP2D6 enzyme influences not only plasma concentrations and the effects of morphine but also those of M6G present during the whole interdialytic period. Our knowledge about the clinical use of codeine in patients with renal failure or HD patients is very limited, and so far, the recommendation is to not use codeine in such patients [16]. Furthermore, there have been some case reports regarding serious side effects of codeine in patients with renal failure [17, 18].

These are several factors that need to be taken into consideration when drugs metabolized by CYPs are prescribed to HD patients. Taking them into account may improve both the efficacy and safety of such drugs and reduce the risk of side effects. Further studies in larger dialysis populations are necessary to optimize the dosing of drugs metabolized by CYP enzymes in this patient population.

## Conclusion

Codeine disposition is affected by both CYP2D6 polymorphism and the HD procedure in patients with ESRD. PMs do not express the CYP2D6 enzyme and are therefore unable to metabolize codeine to the active metabolites morphine and

M6G. Accordingly, we showed that concentrations of M3G and M6G are much higher in EMs compared with PMs. An important observation is that concentrations of glucuronidated metabolites in HD patients are unchanged or even increased until the patients undergo HD, which dramatically reduces the concentration of these metabolites.

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