Eur J Clin Pharmacol (1996) 49 : 503–509

S. H. Sindrup · U. Hofmann · J. Asmussen · G. Mikus
K. Brøsen · F. Nielsen · S. H. Ingwersen
C. Broen Christensen

Impact of quinidine on plasma and cerebrospinal fluid concentrations of codeine and morphine after codeine intake

Received: 7 March 1995 / Accepted in revised form: 29 August 1995

Abstract. *Objective*: The analgesic effect of codeine depends on its O-demethylation to morphine via sparteine oxygenase (CYP2D6) in the liver and presumably also via this enzyme in the CNS. We studied the ability of quinidine, which is a potent inhibitor of CYP2D6, to penetrate the blood brain barrier and its possible impact on codeine O-demethylation in CNS.
Methods: The study comprised 16 extensive and one poor metaboliser of sparteine, who underwent spinal anaesthesia for urinary tract surgery or examination. Eight patients were given an oral dose of 125 mg codeine and 9 patients (including the poor metaboliser) were given 200 mg quinidine 2 h before the same dose of codeine. Plasma and spinal fluid samples were collected 2 h after codeine intake.
Results: Free concentrations of quinidine were 11-times lower in cerebrospinal fluid than in plasma, and ranged from 9–15 nmol · l^{-1}. Morphine concentrations were significantly lower in patients pre-treated with quinidine, both in plasma (median 1.45 nmol · l^{-1}, range 0.74–1.95 nmol · l^{-1} vs 9.86 nmol · l^{-1}, range 4.59–28.4 nmol · l^{-1}) and in cerebrospinal fluid (0.23, 0.16–0.61 nmol · l^{-1} vs 3.63, 0.6–8.09 nmol · l^{-1}). The morphine/codeine concentration ratio in plasma (3.07×10^{-3}, $1.68–3.68 \times 10^{-3}$ vs 19.87×10^{-3}, $9.87–66.22 \times 10^{-3}$) and in cerebrospinal fluid (0.83×10^{-3}, $0.58–1.45 \times 10^{-3}$ vs 7.19×10^{-3}, $2.03–17.7 \times 10^{-3}$) was also lower. The morphine/-codeine concentration ratios were significantly lower in cerebrospinal fluid both without and with quinidine, but the difference between the plasma and spinal fluid ratios was significantly smaller with quinidine than without ($p = 0.0002$).
Conclusion: Quinidine penetrates the blood brain barrier poorly, but quinidine pre-treatment leads to pronounced lowering of the cerebrospinal fluid concentration of morphine after codeine intake. However, the O-demethylation of codeine in CNS may not be totally blocked by quinidine.

Key words CYP2D6, Quinidine, Codeine, morphine, plasma, cerebrospinal fluid

S. H. Sindrup (✉) · K. Brøsen · F. Nielsen
Department of Clinical Pharmacology, Institute of Medical Biology, Odense University, Winsløwparken 19, DK-5000 Odense C, Odense, Denmark

U. Hofmann · G. Mikus
Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany

J. Asmussen
Department of Anesthesiology, Odense University Hospital, Odense, Denmark

S. H. Ingwersen
Pharmacokinetics, Pharmaceutical Division, Novo Nordisk A/S, Måløv, Denmark

C. Broen Christensen
Institute of Pharmacology, Copenhagen University, Copenhagen, Denmark

Introduction

Approximately 7% of a Caucasian population are poor metabolisers (PM) of sparteine and the remainder are extensive metabolisers (EM) (Alvan et al. 1990; Eichelbaum and Gross 1990). The P450 isozyme, CYP2D6, is the source of this genetic polymorphism, and in PM CYP2D6 is absent from the liver (Zanger et al. 1988). The absence of CYP2D6 is caused by mutations in the CYP2D6 gene (Kagimoto et al. 1990; Gaedigk et al. 1991), so it may be concluded that CYP2D6 is not expressed in any tissue or organ in PM. This should also apply to the CNS, where CYP2D6 is probably also expressed in EM (Niznik et al. 1990; Tyndale et al. 1991).

It has been shown that the O-demethylation of codeine to morphine, which accounts for the elimination of about 10% dose of codeine (Adler et al. 1955), co-segregates with the sparteine oxidation polymorphism (Chen et al. 1988; Dayer et al. 1988;

Yue et al. 1989, Sindrup et al. 1990). PM therefore only produce very small amounts of morphine after codeine intake. This apparently impairs the analgesic effect of codeine, since codeine increases the pain threshold to high energy laser stimulation in EM but not in PM (Sindrup et al. 1990).

Quinidine is a potent inhibitor of CYP2D6 (Otton et al. 1983; Brinn et al. 1986). Studies on the impact of quinidine on the analgesic effect of codeine in EM have been equivocal. In one study it was reported that the RIII (nociceptive flexor reflex in biceps femoris muscle) threshold and subjective pain threshold to electric stimulation of the sural nerve were unaltered by 100 mg codeine when the volunteers had been pretreated 10 h previously with 50 mg quinidine (Desmeules et al. 1991). In another study we found that 200 mg quinidine given 3 h before 100 mg codeine apparently reduced the analgesic effect, as measured by changes in pain detection and tolerance threshold to high energy laser stimuli, but it did not extinguish the response (Sindrup et al. 1992). In both studies an almost total blockade of codeine O-demethylation was verified by very low or undetectable levels of morphine in plasma after codeine following quinidine pre-treatment (Desmeules et al. 1991; Sindrup et al. 1992).

The discrepancy between the studies can be explained in various ways. Quinidine has a local analgesic effect (Juan 1977), so the higher quinidine dose (200 **vs** 50 mg) given a few hours (3 **vs** 10 h) before codeine might have interfered with the pain measurements. In combination with a weak effect of non-transformed codeine, this might have been able to increase the pain threshold significantly. Another possible explanation relates to observations indicating that quinidine penetrates the blood brain barrier poorly (Hiatt and Quinn 1945; Agon et al. 1988). Hiatt and Quinn found that cerebrospinal fluid/plasma and brain tissue/plasma concentration ratios of quinidine were 50–100 times lower than liver tissue/plasma ratio in dogs after a 2 h intravenous infusion of quinidine. The positron emission tomography study by Agon et al. (1988) was also performed in dogs and showed a similar relationship between the plasma and brain levels of quinidine. Codeine is O-demethylated to morphine in brain tissue from rats (Chen et al. 1990). It has been suggested, therefore, that the analgesic effect of codeine stems from morphine formed locally in the brain. It is a simple hypothesis that the O-demethylation of codeine in the CNS is catalysed by CYP2D6 expressed in brain tissue (Fig. 1A). If it is assumed that quinidine penetrates the blood brain barrier poorly, then it follows that quinidine will not block brain CYP2D6 and codeine should still have an analgesic effect even when hepatic CYP2D6 is totally blocked (Fig. 1B).

The aim of the present study was to evaluate the ability of quinidine to penetrate the blood brain barrier of humans and the possible impact of quinidine on the cerebrospinal fluid concentration of morphine after codeine intake by humans.

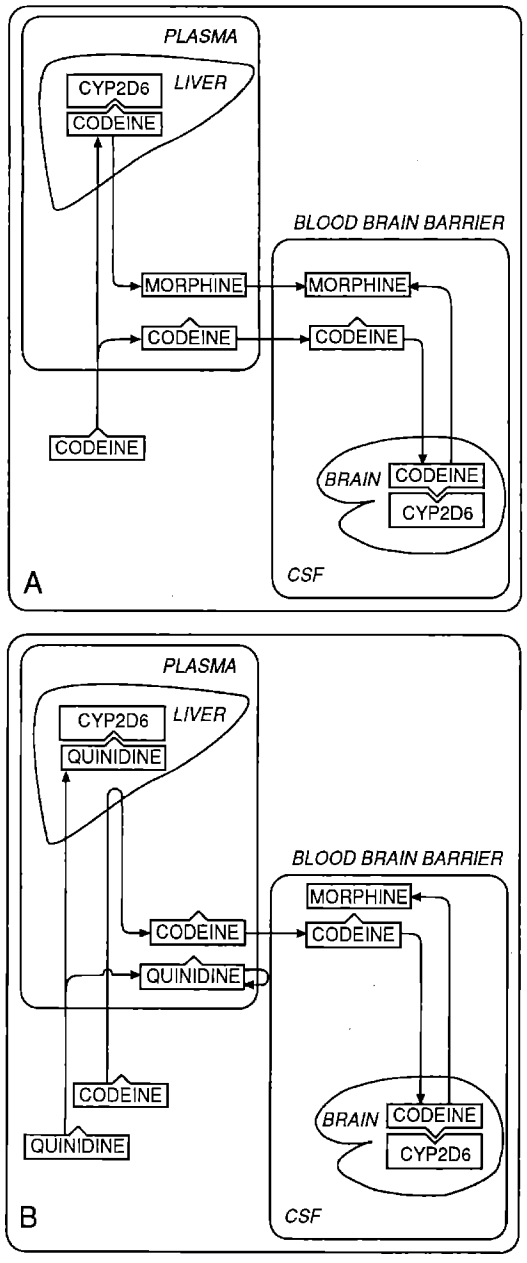

Fig. 1 Hypothetical fate of codeine in the liver and in the CNS and the corresponding contributions to the plasma and cerebrospinal fluid pools of codeine and morphine when codeine is given alone (**A**) or after pre-treatment with quinidine (**B**). Quinidine is a potent inhibitor of the sparteine oxygenase (CYP2D6)

Subjects and methods

Subjects

Twenty six patients undergoing genito-urinary examination and/or surgery in spinal anaesthesia were included in the study. Nine of them were subsequently excluded due to missing plasma samples (6 patients), intake of opioid drugs (2 patients) or use of a drug inhibiting CYP2D6 (1 patient). Demographic details of the 17 patients who completed the study are given in Table 1. The patients gave written informed consent before they were included in the study, and the study was approved by the Ethics Comitteé of the

Counties of Vejle and Fyn (J. no. 92/124) and the National Board of Health (J. no. 2740-171-1992).

Study design and medication

At the time of inclusion the patients were numbered consecutively, counting the first patient as No. 1. Patients with even numbers were given an oral dose of 125 mg codeine 2 h before spinal anaesthesia was to be induced, and those with odd numbers were given an oral dose of 200 mg quinidine (SAD, Copenhagen, Denmark) and an oral dose of 125 mg codeine (SAD, Copenhagen, Denmark), respectively, 4 and 2 h before spinal anaesthesia was induced. The time between codeine dosing and sampling of plasma and cerebrospinal fluid was 2 h ± 15 min. The dose of quinidine of 200 mg was chosen in order to ensure total blockade of hepatic CYP2D6 (Nielsen et al. 1990). Blood and cerebrospinal fluid samples were collected at the time of induction of spinal anaesthesia and the samples (plasma and spinal fluid) were stored at −80°C until analysis. Two or more weeks after the day of study medication, each patient underwent a sparteine test (Brøsen et al. 1985), i.e. they collected urine for 12 h after intake of an oral dose of 100 mg sparteine sulphate (Depasan, Giulini GmbH, Hannover, Germany).

Quinidine assay and equilibrium dialysis

Quinidine in plasma and cerebrospinal fluid was assayed by HPLC (Nielsen et al. 1994). In plasma the limit of quantification was 10 nmol · l^{-1} and the coefficient of variation was 3.3% over the concentration range 0.25–10 μmol · l^{-1}. In cerebrospinal fluid the level of determination appeared to be lower than in plasma, but it was not systematically evaluated.

The free concentration of quinidine in plasma and cerebrospinal fluid was estimated by assay of dialysates obtained by equilibrium dialysis. The dialysis was performed using a Kontron Diapack Model 4000 equipment and cellulose dialysis membranes (Sigma D-9402). The dialysis buffer contained phosphate buffer (9.4 mmol · l^{-1}, pH 7.40), $MgSO_4$ (0.65 mmol · l^{-1}), KCl (5.1 mmol · l^{-1}), and NaCl (127.3 mmol·l^{-1}). Dialysis was performed at 37°C for 24 hours.

Codeine and morphine assay

Codeine and morphine were determined by gas chromatography tandem mass spectrometry (GC-MS-MS) using a TSQ 700 mass spectrometer (Finnigan MAT, Bremen, Germany) coupled to a 5890 II gas chromatograph (Hewlett Packard, Waldbronn, Germany), as described for dihydrocodeine and dihydromorphine (Hofmann et al., 1995). To 1 ml plasma or cerebrospinal fluid 10 ng of morphine-d_3 and 20 ng of codeine-d_3 were added as internal standards. The samples were extracted at pH 9.6 with 6 ml dichloromethane/2-propanol (9:1 v/v), the organic phase evaporated and the residue derivatised with PFPA for 30 min, at 60°C. The derivatising reagent was evaporated and the residue dissolved in 30 μl acetonitrile. 2 μl aliquots were used for GC-MS-MS analysis.

GC was performed on a DB-5 capillary column (25 m, 0.25 mm i.d., 0.25 μm film thickness, J&W Scientific, Fisons, Mainz, Germany) in the splitless mode; the carrier gas was helium at an inlet pressure of 100 kPa. Injections were carried out automatically at 280°C with an A200S autosampler (CTC Analytics, Zwingen, Switzerland). The initial oven temperature of 150°C was held for 1 min, and then it was increased by 35°C · min^{-1} to 250°C. This temperature was held for 4 min, and then it was increased by 30°C · min^{-1} to 300°C. Mass spectrometry was performed in the negative ion chemical ionization (NICI) mode. MS conditions were: source temperature 150°C, methane CI gas pressure 75 Pa, electron energy 120 eV, emission current 200 μA, argon collision cell pressure 133 mPa, collision energy 10 eV. The $[M-20]^-$ ions were used as patent ions (morphine m/z 557, morphine-d_3 m/z 560, codeine m/z 425 and codeine-d_3 m/z 428). The daughter ions were m/z 499 for morphine and morphine-d_3, and m/z 128 for codeine and codeine-d_3.

The limit of quantification was 1 nmol · l^{-1} for codeine and 0.02 nmol · l^{-1} for morphine with a coefficient of variation of 8.1 and 16.9%, respectively.

Data analysis and statistics

Concentrations and ratios were compared between the two treatment groups by the Mann-Whitney test and within the treatment groups by the Wilcoxon's test for paired data. The correlation between morphine and codeine concentrations was tested with Spearman rank correlation.

Results

The sparteine test showed that 16 patients were EM (MR: 0.14–1.2) and one was PM (MR: 173) (Table 1).

Quinidine concentrations

The percentage of protein bound quinidine in plasma ranged from 76 to 91% (median 86%), whereas total and free concentrations were similar in cerebrospinal fluid (Fig. 2). The free concentrations of quinidine in plasma and spinal fluid are detailed in Table 2. Both total and free concentrations of quinidine were significantly higher in plasma (median 735 and 115 nmol · l^{-1}) than in cerebrospinal fluid (11 and 10.3 nmol · l^{-1}) ($P = 0.0039$). The free concentrations of quinidine in plasma was 11-times higher than the concentrations in cerebrospinal fluid (range 8–12.5). This was significantly lower than the corresponding ratio for the total concentrations (median 76, range 55–118) ($P = 0.0039$) (Fig. 2).

Codeine and morphine concentrations

Individual codeine and morphine concentrations in plasma and spinal fluid are given in Table 2, and are shown in Fig. 3. In EM the codeine concentrations did not differ significantly between the patients treated with codeine alone and those pre-treated with quinidine, neither in plasma (median 485 vs 467 nmol · l^{-1}, $P = 0.44$) nor in cerebrospinal fluid (387 vs 308 nmol · l^{-1}, $P = 0.44$). In contrast, morphine concentrations were significantly lower in plasma (9.86 vs 1.45 nmol · l^{-1}, $P = 0.0002$) and in cerebrospinal fluid (3.63 vs 0.23 nmol · l^{-1}, $P = 0.0003$) in patients pretreated with quinidine.

The morphine/codeine concentration ratios in EM were significantly lower after quinidine co-treatment than without it, both in plasma (3.1×10^{-3} vs 19.9×10^{-3}, $P = 0.0002$) and in cerebrospinal fluid

Table 1 Demographic details and study medication for each patient

Patient no.	Sex M: male F: female	Age (y)	[a]Sparteine MR	Concomitant medication	[b]Study medication
1	M	75	1.2	Salbutamol Beclometasone	Q + C
2	M	43	0.14	–	C
3	M	48	0.24	Enalapril	Q + C
4	M	74	0.45	–	C
5	M	71	0.22	–	Q + C
10	M	69	0.28	Paracetamol	C
14	M	75	0.27	Aspirin	C
15	M	64	173	–	Q + C
16	F	68	0.53	Diltiazem	C
17	F	50	0.57	–	Q + C
18	M	77	0.78	–	C
19	M	72	0.22	Hydrochlorthiazide Amiloride	Q + C
21	M	58	0.31	Chlordiazepoxide	Q + C
22	M	70	1.1	–	C
23	M	65	0.79	–	Q + C
24	M	69	0.55	–	C
25	M	69	0.56	–	Q + C

[a]Sparteine MR: Ratio between dehydrosparteine and sparteine in urine collected 12 hours after 100 mg sparteine. MR < 20 defines the extensive metaboliser phenotype and MR ≥ 20 defines the poor metabolizer phenotype.
[b] C: Codeine Q: Quinidine

Table 2 Free concentration of quinidine and total concentration of codeine and morphine in plasma and cerebrospinal fluid 4 hours after an oral dose of 200 mg quinidine and 2 hours after an oral dose of 125 mg codeine. Patients with even numbers were only dosed with codeine

Patient no.	Plasma			Cerebrospinal fluid		
	Quinidine ($nmol \cdot l^{-1}$)	Codeine ($nmol \cdot l^{-1}$)	Morphine ($nmol \cdot l^{-1}$)	Quinidine ($nmol \cdot l^{-1}$)	Codeine ($nmol \cdot l^{-1}$)	Morphine ($nmol \cdot l^{-1}$)
2	–	296	7.41	–	264	4.06
4	–	619	19.93	–	457	8.09
10	–	465	4.59	–	329	1.37
14	–	937	9.67	–	405	0.82
16	–	820	10.81	–	676	3.58
18	–	429	28.4	–	369	5.77
22	–	495	10.04	–	406	3.68
24	–	475	9.23	–	152	0.60
Median	–	485	9.86	–	387	3.63
1	159	530	1.95	15	302	0.21
3	98	358	0.98	8	255	0.18
5	137	453	1.61	11	422	0.61
15[a]	115	441	0.74	10	313	0.18
17	95	535	1.42	9	408	0.37
19	114	475	1.61	14	254	0.24
21	141	478	1.69	13	377	0.37
23	89	536	1.29	10	415	0.40
25	125	458	0.79	10	276	0.16
Median	115	467	1.45	10	308	0.23

[a]Poor metaboliser of sparteine (data not included in determination of median of codeine and morphine values).

(0.8×10^{-3} vs 7.2×10^{-3}, $P = 0.0002$) (Fig. 4). The ratios were lower in spinal fluid than in plasma in both treatment groups ($P = 0.008$). The difference between the spinal fluid and plasma ratios was significantly smaller with than without quinidine ($P = 0.0002$). Morphine in cerebrospinal fluid showed a marginally significant correlation with codeine in cerebrospinal fluid after quinidine pre-treatment ($r_s = 0.68$, $0.10 > P > 0.05$), but not without it ($r_s = 0.38$, $0.50 > P > 0.20$).

The cerebrospinal fluid/plasma ratio of morphine concentrations in EM did not differ between the two treatment groups (0.32×10^{-3} vs 0.21×10^{-3}, $P = 0.51$).

For the single PM patient, who was pre-treated with quinidine, all concentrations and ratios were within the

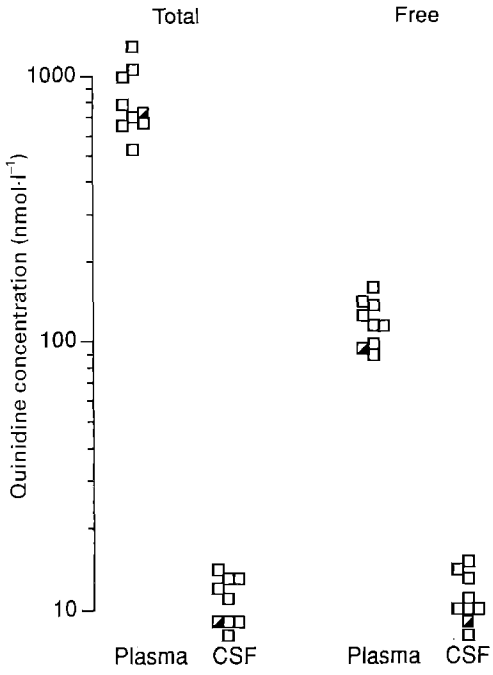

Fig. 2 Total and free concentrations of quinidine in plasma and cerebrospinal fluid (CSF) 4 hours after an oral dose of 200 mg quinidine in 8 extensive (□) and one poor (◪) metaboliser of sparteine

range found in the EM patients pre-treated with quinidine (Figs. 3, 4).

Discussion

The results of this study must be interpreted with caution. First, the single post-dose samples of plasma and spinal fluid can only give a very rough picture of the kinetics. And second, differences in protein content may invalidate comparisons of concentrations and ratios between plasma and spinal fluid.

Quinidine penetration of the blood brain barrier

We found that quinidine penetrated the blood brain barrier poorly in humans, since the free cerebrospinal fluid concentrations of quinidine after a single oral dose were 11-times lower than the corresponding plasma concentrations (Fig. 2). This is in line with the observations previously made in the dog (Hiatt et al. 1945; Agon et al. 1988). However, quinidine does penetrate the barrier and is found at a low concentration (10–15 nmol · l^{-1}) in the cerebrospinal fluid. This level is well below the K_i for quinidine inhibition of CYP2D6 in human liver microsome preparations, which has been reported to be about 60 nM (Otton et al. 1983). However, it may be sufficient to inhibit codeine O-demethylation. The K_m for this process via CYP2D6 is about 150 µmol · l^{-1}, and it has been found

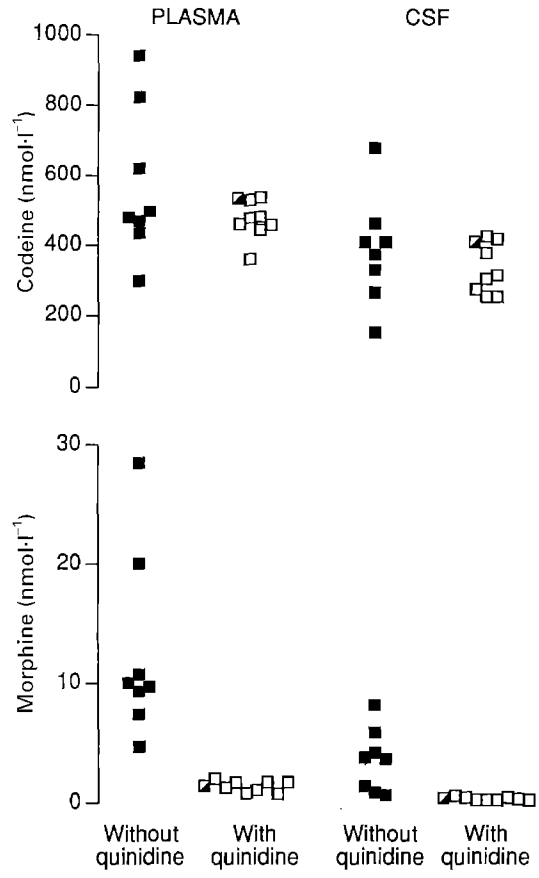

Fig. 3 Individual plasma and cerebrospinal fluid (CSF) concentrations of codeine and morphine in 17 patients two hours after an oral dose of 125 mg codeine without (■) or with (□) oral pretreatment with 200 mg quinidine. One patient was a poor metabolizer of sparteine (◪) and 16 were extensive metabolisers (■,□)

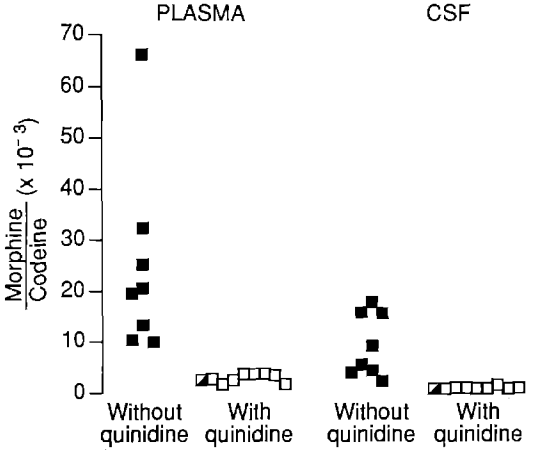

Fig. 4 Individual plasma and cerebrospinal fluid (CSF) morphine/codeine concentration ratios in 17 patients two hours after an oral 125 mg codeine without (■) or with (□) pretreatment with an oral dose of 200 mg quinidine. One patient was a poor metaboliser of sparteine (◪), and 16 were extensive metabolisers (■, □)

that K_i for the inhibition of this process by quinidine is 15 nmol · l^{-1} in human liver microsomes (Dayer et al. 1988). If it were possible to measure codeine

metabolism in brain microsomes, then there is every reason to believe that K_i of the quinidine would be in the same order of magnitude (Otton et al. 1984).

Another important point is that this was a single dose study. The equilibrium between plasma and cerebrospinal fluid might be different in multiple dosage regimens. The well known CNS side effects during chronic treatment with quinidine (Bigger and Hoffman 1990) suggest that quinidine is present in the CNS at pharmacologically active level following a therapeutic dose.

Codeine O-demethylation after quinidine

The study showed that morphine levels both in plasma and cerebrospinal fluid were extremely low when codeine was given after quinidine pre-treatment, and the levels were clearly lower than without quinidine (Fig. 3). Thus, either conversion of codeine to morphine via CYP2D6 in the CNS was greatly inhibited by quinidine, or the local conversion does not contribute much to the amount of morphine in cerebrospinal fluid.

The finding that the cerebrospinal fluid/plasma ratios for morphine were unaltered by quinidine indicates that quinidine does block the central conversion of morphine. However, there was also evidence that conversion in CNS might not have been completely blocked. First, the significantly smaller difference in the morphine/codeine concentration ratio between plasma and cerebrospinal fluid when quinidine pre-treatment was given may indicate that codeine O-demethylation in the CNS contributed relatively more to the total amount of morphine in cerebrospinal fluid after quinidine than without it. And second, this is also indicated by the correlation between morphine and codeine in cerebrospinal fluid with but not without quinidine.

The lower morphine/codeine concentration ratio in cerebrospinal fluid than in plasma found both without and with quinidine pre-treatment might be due to more rapid penetration of the blood brain barrier by codeine than by morphine, since morphine is the more polar of these substances. Such a difference in blood brain barrier penetration has been found in the rat (Oldendorf et al. 1972).

Cerebrospinal fluid morphine concentrations and analgesia

The cerebrospinal fluid concentration of morphine after quinidine pre-treatment appeared to be so low that it could not induce analgesia, even though supraspinal opioid analgesia may be mediated by a subgroup of μ-receptors (μ_1-receptors) for which morphine has a very high affinity (Pasternak and Wood 1986). Further, it is reasonable to consider that the morphine concentration measured in cerebrospinal fluid may not reflect the concentration of morphine at the receptor site. Codeine conversion may take place in close relation to the receptors, as has been shown for N-demethylation of morphine (Fishman et al. 1976), and thereby produce a high morphine concentration there.

Even though the present results are difficult to interpret unequivocally they do support our previous explanation of the partly preserved analgesic effect of codeine when quinidine pre-treatment was given 3 h before codeine (Sindrup et al. 1992). The reason why Desmeules et al. (Desmeules et al. 1991) found total abolition of the analgesic response to codeine after quinidine is not known. It may be important that quinidine was given 10 h before codeine as opposed to 3 h in our study, i.e. the equilibrium between plasma and cerebrospinal fluid quinidine concentrations and binding to CYP2D6 in the CNS may have been different.

We have previously suggested that CYP2D6 in the CNS catalyses the final step in the endogenous synthesis of morphine in humans, since PM lacking this enzyme are less tolerant to tonic pain stimulation (Sindrup et al. 1993). It was later reported that the codeine/morphine ratio in urine was 2-fold higher in PM than in EM, but the difference was not statistically significant (Mikus et al. 1994). However this might represent a Type 2 statistical error, due to high interindividual variability of the codeine/morphine ratios.

In conclusion, quinidine penetrates the blood brain barrier in humans poorly, but quinidine pre-treatment induces pronounced lowering of the cerebrospinal fluid level of morphine after codeine intake. It is possible that the conversion of codeine to morphine in the CNS after codeine administration may not be totally blocked by quinidine.

Acknowledgements Codeine and quinidine tablets were kindly supplied by Amternes Lægemiddelregistreringskontor I/S, Copenhagen, Denmark. The study was financially supported by a grant from the Danish Medical Research Council (No. 12-1654-1).

References

Adler TK, Fujimoto JM, Way EL, Baker EM (1955) The metabolic fate of codeine in man. J Pharmacol Exp Ther 114:251–262

Agon P, Braeckman R, van Haver D, Denutte H, Goethals P, Donche H, Vermullen F, Deman J, Kaufman J.-M (1988) Drug distribution in dog brain studied by positron emission tomography. Biopharmaceut Drug Disp 9:567–577

Alván G, Bechtel P, Iselius L, Gundert-Remy U (1990) Hydroxylation polymorhisms of debrisoquine and mephenytoin in European populations. Eur J Clin Pharmacol 39:533–537

Bigger JT, Hoffman BF (1990) Antiarrhytmic drugs. In: Goodman Gilman A, Rall TW, Nies AS, Taylor P (eds) The pharmacological basis of therapeutics. 8th ed. Pergamon Press, New York, pp 840–873

Brinn R, Brøsen K, Gram LF, Haghfelt T, Otton SV (1986) Sparteine oxidation is practically abolished in quinidine-treated patients. Br J Clin Pharmacol 22:194–197

Brøsen K, Otton SV, Gram LF (1985) Sparteine oxidation polymorphism in Denmark. Pharmacol Toxicol 60:312–314

Chen ZR, Somogyi AA, Bochner F (1988) Polymorphic O-demethylation of codeine. Lancet II:914–915

Chen ZR, Irvine RJ, Bochner F, Somogui AA (1990) Morphine formation from codeine in rat brain: possible mechanism of codeine analgesia. Life Sci 46:1067–1074

Dayer P, Desmeules J, Leemann T, Striberni R (1988) Bioactivation of the narcotic drug codeine in human livers is mediated by the polymorphic monooxygenase catalyzing debrisoquine 4-hydroxylation (cytochrome P450db1/bufl). Biochem Biophys Res Comm 152:411–416

Desmeules J, Gascon M-P, Dayer P, Magistris M (1991) Impact of environmental and genetic factors on codeine analgesia. Eur J Clin Pharmacol 41:23–26

Eichelbaum M, Gross AS (1990) The genetic polymorphism of debrisoquine/sparteine metabolism-clinical aspects. Pharmacol Ther 46:377–394

Fishman J, Hahn EF, Norton BI (1976) N-demethylation of morphine in rat brain is located in sites with high opiate receptor content. Nature 261:64–65

Gaedigk A, Blum M, Gaedigk R, Eichelbaum M, Meyer UA (1991) Deletion of the entire cytochrome P450 CYP2D6 gene as a cause of impaired drug metabolism in poor metabolizers of the debrisoquine/sparteine polymorphism. Am J Hum Genet 48:943–950

Hiatt EP, Quinn GP (1945) The distribution of quinine, quinidine, cinchonine and cinchonidine in fluids and tissues of dogs. J Pharmacol Exp Ther 83:101–105

Hofmann U, Fromm MF, Johnson S, Mikus G (1995) Simultaneous determination of dihydrocodeine and dihydromorphine in serum by gas chromatography/tandem mass spectrometry. J Chromatogr 663:59–65

Juan H (1977) Inhibition of algesic effect of bradykinin and acetylcholine by mepacrine. Naunyn-Schmiedeberg's Arch Pharmacology 301:23–27

Kagimoto M, Heim M, Kagimoto K, Zeugin T, Meyer UA (1990) Multiple mutations of the human cytochrome P450IID6 gene (CYP2D6) in poor metabolizers of debrisoquine. J Biol Chem 265:17209–17214

Mikus G, Bochner F, Eichelbaum M, Horak P, Somogyi AA, Spector S (1994) Endogenous codeine and morphine in poor and extensive metabolisers of the CYP2D6 (debrisoquine/sparteine) polymorphism. J Pharmacol Exp Ther 268: 546–551

Nielsen F, Nielsen KK, Brøsen K (1994) Determination of quinidine, dihydroquinidine, (3s)-3-hydroxyquinidine, and quinidine-N-oxide in plasma and urine by high performance liquid chromatography. J Chromatogr 660:103–110

Nielsen MD, Brøsen K, Gram LF (1990) A dose-effect study of the in vivo inhibitory effect of quinidine on sparteine oxidation in man. Br J Clin Pharmacol 29:299–304

Niznik HB, Tyndale RF, Sallee FR, Gonzales FJ, Hardwick JP, Inaba T, Kalow W (1990) The dopamine transporter and cytochrome P450IID1 (debrisoquine-hydroxylase) in brain: resolution and identification of two distinct [^{3}H]GBR-12935 binding proteins. Arch Biochem Biophys 276:424–432

Oldendorf WH, Hyman S, Braun L, Oldendorf SZ (1972) Blood brain barrier: penetration of morphine, codeine, heroin, and methadone after carotid injection. Science 128: 984–986

Otton SV, Inaba T, Kalow W (1984) Competitive inhibition of sparteine oxidation in human liver by beta-adrenoceptor antagonists and other cardiovascular drugs. Life Sci 34:73–80

Pasternak GW, Wood PJ (1986) Multiple mu opiate receptors. Life Sci 38:1889–1898

Sindrup SH, Brøsen K, Bjerring P, Arendt-Nielsen L, Angelo HR, Larsen U, Gram LF (1990) Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not in poor metabolizers of sparteine. Clin Pharmacol Ther 48:686–693

Sindrup SH, Arendt-Nielsen L, Brøsen K, Bjerring P, Angelo HR, Eriksen B, Gram LF (1992) The effect of quinidine on the analgesic effect of codeine. Eur J Clin Pharmacol 42:587–592

Sindrup SH, Poulsen L, Brøsen K, Arendt-Nielsen L, Gram LF (1993) Are poor metabolisers of sparteine/debrisoquine less pain tolerant than extensive metabolisers. Pain 53:335–339

Tyndale RF, Sunahara R, Inaba T, Kalow W, Gonzales FJ, Niznik HB (1991) Neuronal cytochrome P450IID1 (debrisoquine/sparteine-type): potent inhibition of activation by (−)-cocaine and nucleotide sequence identity to human hepatic P450 gene CYP2D6. Mol Pharmacol 40:63–68

Yue QY, Svensson J-O, Alm C, Sjöqvist F, Säwe J (1989) Codeine O-demethylation co-segregates with polymorphic debrisoquine hydroxylation. Br J Clin Pharmacol 28:639–645

Zanger UM, Vilbois F, Hardwick J, Meyer UA (1988) Absence of hepatic cytochrome P450bufI causes genetically deficient debrisoquine oxidation in man. Biochemistry 27:5447–5454