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L. Poulsen · K. Brøsen · L. Arendt-Nielsen · L. F. Gram
K. Elbæk · S. H. Sindrup

Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects

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Abstract *Objective*: Codeine O-demethylation to morphine is catalysed by the genetic polymorphic sparteine oxygenase (CYP2D6). The objective of the present study was to assess the analgesic effect of codeine on different types of experimental pain in relation to sparteine phenotype.
Methods: Fourteen extensive (EMs) and 14 poor metabolizers (PMs) of sparteine completed a randomized, double-blind, three-way, cross-over study with a single oral dose of codeine (75 or 100 mg) against morphine (20 or 30 mg) and placebo. Pain tests performed before and 1, 2, 3, and 4 h after medication included the cold pressor test and pain thresholds for heat and pressure stimulation. Adverse effects were rated by a structured interview.
Results: After morphine, morphine and morphine-6-glucuronide were present in equal amounts in plasma of PMs and EMs. After codeine, neither morphine nor morphine-6-glucuronide could be detected in 13 of the 14 PMs, whereas at least one of the compounds could be detected in all EMs. Peak pain and discomfort rated on a VAS scale during the cold pressor test were significantly reduced by morphine in both EMs and PMs, with a median peak change of 8.5 and 7.0 mm, respectively, for peak pain, and 11.5 and 15.5 mm, respectively, for discomfort. Codeine only reduced these pain measures significantly in EMs, with a median peak change of 5.5 mm for peak pain and 10.5 mm for discomfort. Pain detection and tolerance thresholds to heat and pressure were not consistently altered by either morphine or codeine. In PMs, adverse effects were significantly more pronounced on morphine than on codeine and only showed a slight difference between codeine and placebo. In EMs, there was no difference between codeine and morphine and more pronounced adverse effects on both drugs as compared to placebo.
Conclusion: This study confirms that codeine O-demethylation depends on CYP2D6; it shows that the 6-glucuronidation of morphine is independent of CYP2D6; it supports the theory that the analgesic effect of codeine depends on its O-demethylation; and it indicates that this is probably also the case for the adverse effects. The resuls lend no support to the suggestion of a non-opioid analgesic effect of codeine.

Key words CYP2D6, Codeine, Morphine; pharmacokinetics, analgesic effect, adverse effects

L. Arendt-Nielsen
Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark

K. Elbæk
Clinical Research and Development, Nycomed Pharma, Copenhagen, Denmark

L. Poulsen · K. Brøsen · L. F. Gram · S. H. Sindrup (✉)
Department of Clinical Pharmacology,
Institute of Medical Biology, Odense University,
Winsløwparken 19, DK-5000 Odense C, Denmark
Tel.:(66) 158-600, ext. 4788; Fax: (66) 133-3479

Introduction

Codeine is eliminated primarily by glucuronidation, whereas O-demethylation to morphine and N-demethylation to norcodeine are minor elimination pathways, each accounting for about 10% of the dose [1]. The O-demethylation co-segregates with the genetic sparteine/debrisoquine polymorphism [2–4]. CYP2D6, which is the source of this polymorphism, is present in tissues of extensive metabolizers (EMs) of sparteine, whereas it is absent in poor metabolizers (PMs) [5], who make up about 7% of Caucasians [6]. Accordingly, PMs of sparteine are practically unable to metabolize codeine to morphine.

More than 40 years ago, it was suggested that the analgesic effect of codeine was mediated by its metabolite morphine [7]. This view was later supported by experiments showing that codeine has a much lower affinity for the μ-opioid receptor than morphine [8].

We have recently addressed this problem by exploiting the fact that the conversion of codeine to morphine depends on the CYP2D6. In 12 EMs and 12 PMs of sparteine, we found that a single oral dose of 75 mg codeine increased pinprick pain thresholds to high-energy laser stimuli in the EMs but not in the PMs [9]. Further, pre-treatment with the potent CYP2D6 inhibitor quinidine seems to abolish the analgesic effect of codeine [10], although this is controversial [11]. This indicates that 1 in every 14 patients treated with codeine and patients treated with potent CYP2D6 inhibitors might not benefit from the drug with respect to pain relief.

The hypothesis of the present randomized, double-blind, placebo-controlled, three-way, cross-over, single-dose study in EMs and PMs of sparteine was that interphenotype differences in pharmacokinetics and analgesic effect of codeine do exist, but there could be a dissociation with respect to pain modality. Further, side effects could be caused mainly by codeine itself. The study aimed at further exploring the interphenotype differences in pharmacokinetics and analgesic effect as evaluated by different experimental pain models related to different pain modalites, and at testing for differences in adverse effects. Morphine was included as a positive control, since there is a chance that the lack of effect of codeine in PMs in our previous study could be related to other factors than lack of morphine formation from codeine. For example, by coincidence, the PM sample may have included a high fraction of subjects showing no response to analgesics in the pain tests or doing inappropriately unstable tests. Further, by inclusion of pain models that are relatively insensitive to opioids, non-opioid analgesic effects of codeine were searched for.

Subjects and methods

Subjects

Fourteen EMs and 14 PMs of sparteine, who were comparable with respect to age, body weight and sex (Table 1), were recruited among approximately 1600 healthy subjects that had previously been phenotyped with respect to the sparteine oxidation polymorphism at the Department of Clinical Pharmacology, Odense University. A metabolic ratio between 12-h urinary recovery of sparteine and dehydrosparteines higher than 20 defined the PM phenotype and a metabolic ratio lower than 20 defined the EM phenotype [12]. In EMs, the median metabolic ratio was 0.34 (range 0.17–1.5). The volunteers were healthy according to history and clinical examination and were not treated with any drug (except some of the females taking oral contraceptives). Alcohol and other analgesics were not allowed for 24 h within study days and during experiments. The present sample size was chosen with reference to previous studies detecting analgesic effect of different drugs in the pain models [13, 14].

Table 1 Demographic details and drug doses fro the extensive (EM) and poor (PM) metabolizers of sparteine participating in the study

	E:M	P:M
Number	14	14
Male/female	6/8	6/8
Age[a] (years)	22.8 (20–28)	22.8 (21–25)
Body weight[a] (Kg)	64 (50–78.5)	66.5 (54–88)
Drug dose		
Morphine 30 mg, codeine 100 mg	8	10
Morphine 20 mg, codeine 75 mg	6	4

[a]Median (range)

Design and medication

Each phenotype was investigated as a separate group. The study design for each group was randomized, double-blind and three-way cross-over with a single oral dose of codeine against single oral doses of placebo (negative control) and morphine (positive control). Randomization for each group was carried out in blocks of six including the six possible treatment sequences. Thus, in the EM group three subjects were treated in each of the treatment sequences codeine-placebo-morphine and placebo-codeine-morphine, whereas only two subjects were treated in each of the four other sequences. For the PM group the treatment sequences codeine-morphine-placebo and placebo-morphine-codeine included three subjects. All study sessions started at 0830 to 0930 hours. Volunteers weighing more than 60 kg were given 100 mg codeine and 30 mg morphine, whereas volunteers weighing less than 60 kg were given 75 mg codeine and 20 mg morphine (Table 1). A double-dummy technique was used since codeine (25 mg; Nycomed-DAK, Copenhagen) and identical codeine-placebo tablets were different from morphine (10 mg; Nycomed-DAK, Copenhagen) and identical morphine-placebo tablets. The same number of tablets (four codeine or codeine-placebo tablets plus three morphine or morphine-placebo tablets or for volunteers weighing less than 60 kg: three and two of the same tablets) were given on each of the three study days. Pain tests as described below were performed before, and 1, 2, 3 and 4 h after medication and blood for drug level measurements was collected after each series of pain measurements. The post-medication period of observation of adverse effects was 5 h. The study days were separated by at least 1 week for washout.

Pain tests

Cold pressor test (*tonic pain*)

The left hand was immersed into ice-chilled water [0.9 (0.3)°C] that was continuously stirred by a pump. After 2 min of immersion, or sooner if the pain was considered intolerable, the subjects removed their hand from the water. Pain intensity was continuously rated by an electronic visual analog scale coupled to a pen recorder. From the printouts obtained, the peak-pain intensity score and the area under the pain intensity time curve were determined [13]. Immediately after the test, the subjects rated the discomfort experienced (i.e. the overall feeling of unpleasantness) during the test by use of a visual analog scale.

Heat pain thresholds (*phasic pain*)

Heat pain detection and heat pain tolerance thresholds on the volar aspect of the right (detection) and the left (tolerance) wrist were determined by use of a computerized version of the Thermotest (Somedic AB, Stockholm, Sweden) by the method described by Brennum et al. [15]. The thermode consisted of series-coupled Peltier-elements and measured 25×50 mm. For determination of both heat pain detection and heat pain tolerance, a baseline

temperature of 35°C, 1°C·s^{-1} rate of change and a cutoff limit of 52°C were applied. By pressing a button, the subject indicated when the pertinent threshold was reached. Each threshold was calculated as the average of five determinations performed with intervals of about 10 s between stimulations.

Pressure pain thresholds (*phasic pain*)

Pressure pain detection and pressure pain tolerance thresholds were determined on the middle phalanx of the second (detection) and third (tolerance) finger of the right hand with an electronic pressure algometer (Somedic AB, Stockholm, Sweden) by the method described by Brennum et al. [15, 16]. A 28-mm^2 circular probe was loaded with 1.1 N·s^{-1} and the subject indicated when the pertinent threshold was reached. The cutoff limit was 1400 kPa. Each threshold was calculated as an average of five determinations with about 10 s intervals between stimulations.

Adverse effects

Each symptom (sedation, dry mouth, dizziness, nausea, headache, relaxation, euphoria) experienced during the 5-h observation period was noted by the volunteers (onset, duration and severity). At the end of the observation period, the severity of each symptom was rated (0 = not present, 1 = mild, 2 = moderate and 3 = pronounced) by the investigator on the basis of an interview with the volunteer.

Plasma drug concentrations

The plasma concentrations of codeine, morphine and morphine-6-glucuronide were determined by two separate HPLC methods. The analysis of codeine was performed using a reversed-phase HPLC method with fluorometric detection. The limit of quantitation was 50 nmol·l^{-1}. At spiked concentrations of 615 and 246 nmol·l^{-1}, the accuracy was 104% and 97%, and the coefficient of variation was 7.2% and 6.7%, respectively. Morphine and morphine-6-glucuronide were assayed with on-line sample clean-up and electrochemical detection. The limit of quantitation was 4 and 10 nmol·l^{-1}, respectively. At morphine concentrations of 5.3, 13.3 and 53.3 nmol·l^{-1}, the accuracy was 111%, 97% and 97%, and the coefficient of variation was 17.5%, 7.6% and 6.4%, respectively. At morphine-6-glucuronide concentrations of 20, 40 and 200 nmol·l^{-1}, the accuracy was 94%, 90% and 97%, and the coefficient of variation was 15.0%, 15.6% and 10.4%, respectively.

Data analysis and statistics

The peak change from the premedication value on placebo, codeine and morphine was identified and compared by use of the Wilcoxon's test for paired differences. Analysis of differences in area under concentration time curves from time 0 to 4.5 h (AUC[0→4.5 h]) were carried out by use of the Mann-Whitney (between phenotypes, within drugs) and Wilcoxon's (within phenotypes, between drugs) tests. The frequency of subjects experiencing side effects was compared by use of the McNemar change test (within phenotypes, between drugs). For each side effect, the severity score was multiplied by the duration to obtain an overall measure of the pertinent side effect. Further, the total side effect burden on each subject was calculated as the sum of the severity score times duration of the seven different adverse effects registered. The differences, in this measure between the drugs were compared in each phenotype with the Wilcoxon's test for paired differences.

The study was approved by the regional Ethics Committee of the counties of Vejle and Fyn (j.no. 91/101) and the Danish National Board of Health (j.no. 2740–181–1991). The subjects gave their written consent to participation on the basis of verbal and written information.

Results

Pharmacokinetics

Interindividual concentrations of morphine and morphine-6-glucuronide after morphine, and of codeine, morphine and morphine-6-glucuronide after codeine are shown in Figs. 1 and 2.

After morphine, median (range) of AUC[0→4.5 h] for morphine and morphine-6-glucuronide was 92 (32–176) nmol·l^{-1}·h, and 601 (371–830) nmol·l^{-1}·h, respectively, for EMs, and 82 (31–154) nmol·l^{-1}·h and 555 (356–792) nmol·l^{-1}·h, respectively, for PMs. There was no statistically significant interphenotype difference in these AUCs (P = 0.29 and 0.73) or in the ratios between morphine-6-glucuronide and morphine AUC (range for EMs: 3.4–13.3 and for PMs: 3.8–4.3, P = 0.19).

After codeine, AUC[0→4.5 h] for codeine for EMs and PMs was 1427 (954–2795) nmol·l^{-1}·h and 1569 (1029–2510) nmol·l^{-1}·h, respectively (P = 0.67). In PMs, morphine and morphine-6-glucuronide could not

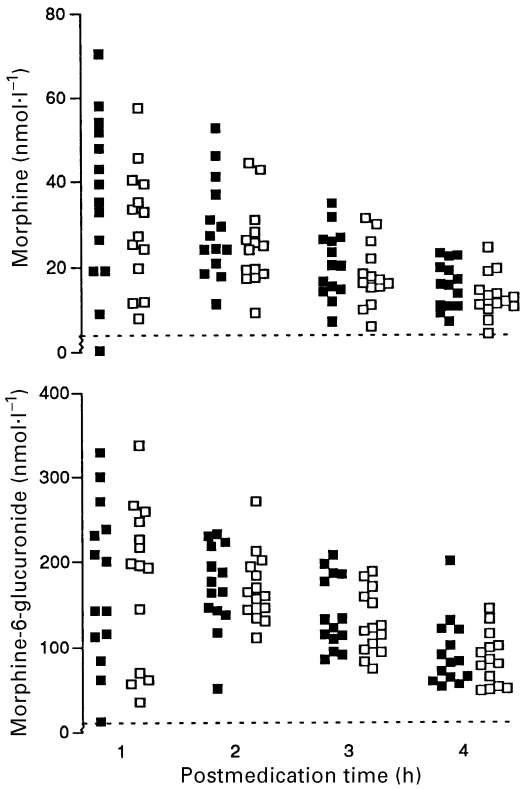

Fig. 1 Individual plasma concentrations of morphine and morphine-6-glucuronide in 14 extensive (■) and 14 poor (□) metabolizers of sparteine after an oral dose of 20 or 30 mg morphine

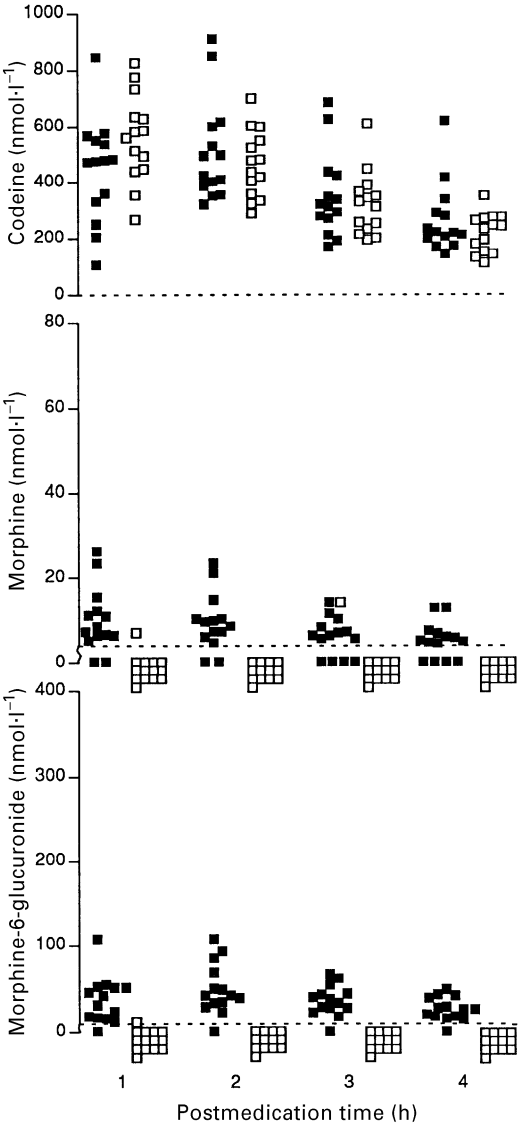

Fig. 2 Individual plasma concentrations of codeine, morphine and morphine-6-glucuronide in 14 extensive (■) and 14 poor (□) metabolizers of sparteine after an oral dose of 75 or 100 mg codeine

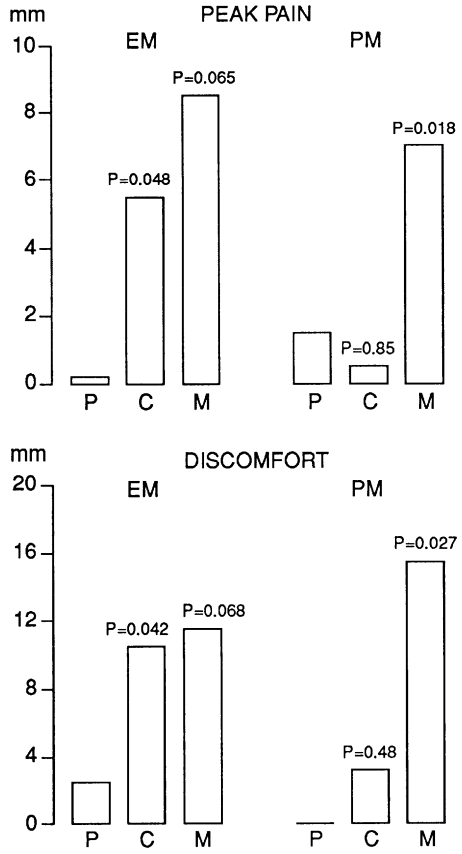

Fig 3 Median of the peak changes in peak pain and discomfort during the cold pressor test in extensive (EM) and poor (PM) metabolizers of sparteine on placebo (P), codeine (C) and morphine (M). *P* values for comparison between the effect of each drug and placebo are given (Wilcoxon's test for paired differences)

be detected in plasma after codeine intake except for very low levels at one measurement in one subject. In EMs, morphine was detectable in all subjects except one, and morphine-6-glucuronide was detectable in all subjects at least at one measurement. The AUC[0→4.5 h]s in EMs were determined to be 28 (0–75) $nmol \cdot l^{-1} \cdot h$ for morphine and 139 (15–306) $nmol \cdot l^{-1} \cdot h$ for morphine-6-glucuronide. In EMs, the AUCs for both morphine and morphine-6-glucuronide were significantly lower during codeine than during morphine ($P = 0.0001$). In EMs, the ratio between AUC[0→4.5 h] for morphine-6-glucuronide and morphine on codeine (4.8, 3.0–21.2) was not different from this ratio after administration of morphine (5.7, 3.4–13.3) ($P = 0.17$).

Pain test

The peak change in peak pain and discomfort during the cold pressor test in EMs and PMs is shown in Fig. 3. In EMs, peak pain was significantly reduced by both codeine ($P = 0.048$) and morphine ($P = 0.065$) as compared to placebo. In PMs, there was a clear reduction on morphine ($P = 0.018$), but no effect on codeine ($P = 0.85$). The same pattern was seen for the discomfort ratings, i.e. in EMs a significant reduction on both codeine ($P = 0.042$) and morphine ($P = 0.068$), and in PMs a clear effect on morphine ($P = 0.0027$) but no effect on codeine ($P = 0.48$). Pain area during the cold pressor test was unaltered by codeine in EMs ($P = 0.27$) and by codeine ($P = 0.15$) and morphine ($P = 0.14$) in PMs. There was a significant reduction in EMs on morphine ($P = 0.0085$). Heat pain thresholds were not changed by either codeine or morphine in any of the phenotypes (Table 2). The pressure pain detection thresholds were not altered by either codeine or morphine, except for a marginal effect of morphine in PMs ($P = 0.079$) (Table 2). There was a higher peak increase in pressure pain tolerance thresholds on morphine than on placebo in both EMs ($P = 0.018$) and PMs

Table 2 Median (95% confidence interval) of peak increase in pain thresholds

		Placebo	Codeine	Morphine	*P* value[a]	
					Codeine	Morphine
Extensive metabolizers (*n* = 14)						
Heat pain (°C)	Detection	0.3 (−0.7–0.8)	0.4 (0.1–1.3)	0.3 (−0.5–0.9)	0.43	0.50
	Tolerance	0.6 (−0.2–1.1)	0.5 (0.1–1.6)	0.9 (0.1–1.6)	0.67	0.23
Pres. pain (kPA)	Detection	19 (−15–39)	24 (−19–72)	25 (−19–69)	0.19	0.50
	Tolerance	3 (−19–43)	28 (−3–77)	41 (7–81)	0.13	0.018
Poor metabolizers (*n* = 14)						
Heat pain (°C)	Detection	1.0 (−0.3–1.6)	0.4 (−0.4–0.9)	0.7 (0.1–2.2)	0.12	0.98
	Tolerance	0.4 (−0.3–0.9)	0.6 (−0.4–1.7)	0.6 (0.1–1.2)	0.60	0.55
Pres. pain (kPA)	Detection	27 (−15–57)	38 (−8–93)	51 (16–111)	0.43	0.079
	Tolerance	14 (−28–60)	61 (0–95)	73 (9–105)	0.13	0.068

Each drug compared to placebo, Wilcoxon's test for paired differences

Table 3 Number of volunteers reporting different adverse effects on a single oral dose of 20 mg/30 mg morphine, 75 mg/100 mg codeine or placebo

	Extensive metabolizers (*n* = 14)			Poor metabolizers (*n* = 14)		
Adverse effect	Morphine	Codeine	Placebo	Morphine	Codeine	Placebo
Sedation	11	7	3	9	6	3
Dry mouth	4	8	2	7	3	0
Dizziness	1	3	1	2	1	0
Nausea	2	1	0	2	0	0
Headache	0	0	0	1	1	1
Relaxation	1	2	0	1	1	0
Euphoria	1	0	0	0	0	0

Table 4 Median (95% confidence interval) for the total amount of adverse effects

	Extensive metabolizers		Poor metabolizers	
	Side effect total[a] (points × min)	*P*-value[b]	Side effect total[a] (points × min)	*P*-value[b]
Placebo	0.4 (0–195)		0.2 (0–6)	
Morphine	270 (105–630)		310 (120–810)	
Codeine	285 (115–820)		37.5 (0–650)	
Morphine vs. placebo		0.0005		0.001
Codeine vs. placebo		0.012		0.055
Codeine vs. morphine		0.88		0.0093

[a] Sum of severity score × duration for seven side effects (sedation, dry mouth, dizziness, nausea, headache, relaxation, and euphoria)
[b] Wilcoxon's test for paired differences

(*P* = 0.068), whereas this was not the case with codeine for any of the phenotypes (Table 2).

Adverse effects

The number of EMs and PMs experiencing different adverse effects are detailed in Table 3. The number of EMs that had any adverse effects were nearly identical on morphine and codeine. Five PMs had no adverse effects on codeine despite their having adverse effects on morphine, and there were no PMs with adverse effects on codeine without also having adverse effects on morphine ($0.05 < P < 0.10$). The total adverse effect burden for EMs and PMs during each of the treatments is given in Table 4. In EMs, the total adverse effect measure was higher on morphine and codeine than on placebo (*P* = 0.0005 and 0.012), and there was no difference between codeine and morphine (*P* = 0.88). In PMs, there was a significantly higher total adverse effect measure on morphine (*P* = 0.001 and 0.009) than on placebo and codeine, which only showed a borderline significant difference from placebo (*P* = 0.055).

Discussion

Pharmacokinetics

The co-segregation of codeine O-demethylation with the sparteine oxidation polymorphism [2–4] was clearly

confirmed in this study, since after codeine, measurable amounts of morphine or morphine-6-glucuronide were found in all EMs, whereas these metabolites could only be detected at a low level in one PM subject. The relationship between morphine-6-glucuronidation and the polymorphism has not previously been studied. Comparable ratios between morphine-6-glucuronide and morphine after morphine in the two phenotypes indicate that this metabolic pathway is independent of CYP2D6 in agreement with previous studies on the glucuronidation of 8-hydroxy-clomipramine [17].

In EMs, there was no difference in the ratio between morphine-6-glucuronide and morphine after morphine and after codeine. However, the plasma concentrations of morphine and morphine-6-glucuronide were clearly lower (a factor 3–4 difference in median concentration) after codeine than after morphine although assumed equipotent analgesic doses were used [18]. Old data on the oral morphine vs. oral codeine analgesic potency indicate a difference by a factor of 6 [19], but this still would not explain the observed higher difference in plasma concentrations.

Analgesic effect

The reduced peak pain and discomfort during the cold pressor test in both phenotypes when morphine was given proves the sensitivity of this test in detecting opioid analgesia and suggests that the EMs and PMs selected for this trial were qualified. The suggestion that the analgesic effect of codeine depends on the genetic polymorphic O-demethylation of codeine to morphine was supported, since in EMs there was an analgesic effect of both codeine and morphine, whereas in PMs there was a clear dissociation between the effect of the two drugs with no effect of codeine.

The phasic pain models applied, and especially pain detection thresholds in these models, are known only to show a subtle response to opioids [20–22]. In line with this, we found no effect on detection thresholds of the drugs in any of the two phenotypes except for a marginal increase in pressure pain detection in PMs on morphine. The pain tolerance thresholds in the phasic pain models have recently been found to be able to detect the analgesic effect of epidurally applied morphine [23], and we found a significant effect of morphine given orally on the pressure pain tolerance thresholds. It is possible that these phasic pain models could have shown significant changes with an increased sample size. However, in this study, these thresholds cannot be used to evaluate the role of morphine in codeine analgesia, since codeine did not induce any changes in these thresholds in any of the two phenotypes. In general, the lack of effect of codeine in the phasic pain models lends no support to a non-opioid analgesic effect of codeine itself. The thresholds determined in these tests have been shown to be increased by, e.g. the tricyclic antidepressant imipramine [14], i.e. a non-opioid analgesic.

In general, the results may have been more clear cut if we had used the same doses in all subjects. In EMs, for example there was a tendency of lack of effect of codeine on the cold pressor peak pain for subjects treated with the lower dose as contrasted by an effect in all subjects treated with the higher dose. A similiar pattern was not seen in PMs.

Adverse effects

In PMs, adverse effects after codeine were only slightly different from those after placebo and significantly less pronounced than those after morphine. In EMs, adverse effects after codeine and after morphine were not different, but significantly more pronounced than after placebo. It is thus indicated that the side effects of codeine are mainly related to the metabolically formed morphine and/or morphine metabolites. The adverse effects observed were as expected for opioid drugs, but the present material was too small to do extensive analyses of the adverse effect profile of codeine in PMs as compared to morphine in PMs, and to codeine and morphine in EMs. However, there appeared not to be major differences (Table 3).

Relations between pharmacokinetics and analgesic

The marked difference in the plasma concentrations of morphine and morphine-6-glucuronide after morphine and codeine was to be expected due to the interindividual differences in biotransformation. In spite of that, the overall impression was that there was only a slightly better analgesic response on morphine than on codeine in EM. The latter complies with the fact that we chose equipotent doses of morphine and codeine [18]. Equipotency despite marked differences in plasma concentrations of morphine and morphine-6-glucuronide may not be in conflict with the suggested effect of codeine through metabolically formed morphine. Codeine apparently penetrates the blood-brain barrier more easily than morphine [24], and it has been suggested that conversion of codeine to morphine locally in the CNS may be of major importance for codeine analgesia [25]. This local conversion of codeine to morphine could possibly take place via CYP2D6 [11, 26], which may be expressed in brain tissue [26–28], although it is mainly regarded as a hepatic enzyme. Thus, the plasma concentrations may not reflect the concentrations near the opioid receptors in the CNS and may therefore be totally irrelevant for the analgesic effect of codeine.

This study comprised healthy volunteers given single oral drug doses. It cannot be excluded that the interdrug and interphenotype relations in analgesic effect and adverse effects of codeine and morphine are

different in pain patients on single or multiple drug doses. This should be investigated in future clinical studies.

Conclusion

This study confirmed that the O-demethylation of codeine to morphine depends on CYP2D6 and showed that the 6-glucuronidation of morphine is independent of this enzyme. Analgesia, as evaluated by the cold pressor test, was in line with the suggestion that codeine analgesia depends on the conversion of codeine to morphine. The other pain variables showed no consistent response on morphine and/or codeine, and these variables could therefore not be used to judge this relationship. It was indicated that codeine adverse effects appeared mainly to be related to the metabolically formed morphine.

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