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PHARMACODYNAMICS

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Codeine in post-operative pain

Study of the influence of sparteine phenotype and serum concentrations of morphine and morphine-6-glucuronide

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Abstract *Objective*: Within the past decade, human experimental pain studies have supported the 50-year-old hypothesis that codeine is a prodrug, which has to be converted to morphine to exert an analgesic effect. This study aimed at evaluating the impact of sparteine phenotype and serum concentrations of morphine on the efficacy of codeine in post-operative pain.
Methods: Eighty-one patients with a pain rating of 3 or more on a 0–10 numerical rating scale 0.5 h after surgery were included in the study. The patients were given an oral dose of 100 mg codeine and rated pain with the numerical rating scale 0.5 h and 1 h after medication. Blood for determination of serum concentration of codeine and its metabolites was collected 1 h after medication, and a 12-h urine sample after administration of 100 mg sparteine was used to determine the sparteine phenotype.
Results: Eight patients were poor metabolizers and 66 were extensive metabolizers of sparteine, while the urine samples for the remaining seven patients were lost. In 22 patients, including the eight poor metabolizers, the serum concentrations of both morphine and morphine-6-glucuronide (M6G) were below the limit of determination of the assay, i.e. 1.5 nmol·l^{-1} and 2 nmol·l^{-1}, respectively. A sum of the concentration of these two substances below 10 nmol·l^{-1} was found in an additional eight patients. The sum of differences between pre- and post-operative pain ratings did not differ between the two phenotypes ($P = 0.60$), whereas the 30 patients with serum concentrations of morphine plus M6G below 10 nmol·l^{-1} had a marginally significant lower sum than the 51 patients with higher levels of these substances (median 1.5 vs 2.5, $P = 0.058$).
Conclusion: A low serum concentration of morphine and M6G seems to be common in patients treated with codeine for post-operative pain, and low concentrations of these active substances may be related to decreased efficacy of codeine.

Key words Post-operative pain · Codeine

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Introduction

About 50 years ago, it was hypothesized that codeine has to be converted to morphine in order to exert its analgesic effect (Sanfilippo 1948). Later, receptor binding studies supported this view, since it was found that the affinity of codeine for the μ-opioid receptor is a factor 3000× lower than morphine's affinity for this receptor (Pert and Snyder 1973). Human experimental studies have given further support to the hypothesis. The O-demethylation of codeine to morphine depends on the enzyme CYP2D6 (Yue et al. 1989), which exhibits genetic polymorphism (Eichelbaum et al. 1979). Ninety-three per cent of the Caucasian population has the enzyme (extensive metabolizers of sparteine), while it is absent in the remaining 7% (poor metabolizers of sparteine; Alván et al. 1990; Zanger et al. 1988). In extensive metabolizers of sparteine, pain thresholds to high-energy laser light stimulation are increased by codeine, whereas this is not the case in poor metabolizers, who are practically unable to metabolize codeine to morphine (Sindrup et al. 1990). A more recent study with other human experimental pain models has shown the same pattern with respect to the analgesic effect of codeine in extensive and poor metabolizers of sparteine, but with no inter-phenotype difference in the effect of morphine (Poulsen et al. 1996).

The clinical implications of these findings have not previously been tested. In the present study, we

attempted to evaluate the impact of the sparteine phenotype and serum concentrations of morphine on the post-operative analgesia of codeine.

Materials and methods

Patients aged 20–80 years referred to the Department of Surgery at Faaborg Hospital for minor surgery (varicose veins, hernia, spermatocele etc.) who were to be anaesthesized by spinal analgesia were eligible for the study. Patients treated with drugs known to inhibit CYP2D6 [quinidine and some other antiarrhythmics, tricyclic antidepressants, some neuroleptics, some selective serotonin inhibitors (Brøsen and Gram 1989; Brøsen 1993)] were not included. The study was approved by the ethics committee for the counties of Fyn and Vejle and the National Board of Health. Two hundred and thirty-six patients agreed to participate in the study after being given verbal and written information at a pre-surgery screening visit to the hospital (Fig. 1). These patients performed a sparteine test (Brøsen et al. 1985), i.e. they collected urine for 12 h after an oral dose of 100 mg sparteine. Urine aliquots were kept frozen until analysis at some time after the day of surgery. Sparteine and its dehydro-metabolites were determined by gas chromatography and a metabolic ratio (sparteine/sum of dehydrosparteines) <20 defined the extensive metabolizers and a ratio ≥ 20 defined the poor metabolizers (Brøsen et al. 1985). Eight patients did not turn up for surgery and it was not possible for another 29 to go through the study procedure for logistical reasons. Eleven patients withdrew their consent to participate on the day of surgery.

The sparteine phenotype of the patients was not known by either the patients or the staff that took care of them during the study, since urine samples from the sparteine tests were first analysed after the day of codeine medication.

The spinal blocks were performed with lignocaine 2% 80–100 mg corresponding to a block level of Th_8–Th_{10}. In 15 patients, it transpired during surgery that spinal analgesia was insufficient and therefore general anaesthesia was used. Two patients with extreme nervousness during surgery were treated with sedatives intravenously. Eighty-eight of the remaining patients did not experience pain of an intensity that required treatment (<3 on a 0–10 point numerical rating scale) 0.5 h after surgery or were given supplementary systemic analgesics at the end of surgery.

This left 83 patients who were given an oral dose of 100 mg codeine. These patients performed pain ratings on the 11-step 0 (no pain) to 10 (worst possible pain) numerical scale before, and 0.5, 1, 2, 3 h and 4 h after medication. Escape medication (paracetamol, morphine, tramadol etc.) was given on request. One hour after medication, blood for determination of codeine and its metabolites was collected.

The concentrations of codeine, morphine, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G) were determined by two different HPLC methods. Codeine was extracted from plasma by means of an organic phase consisting of *n*-hexane and dichloromethane (2:1). This procedure was carried out twice. Subsequently, the organic phase was evaporated under a stream of nitrogen at 35 °C. The residue was dissolved in 0.125 ml of the mobile phase and 0.1 ml was injected onto the reversed-phase column (Bondclone 10 C18). Detection was carried out by a fluorescence detector (Jasco FP 920) and calculations were done using a Merck D-2000 integrator. Fluorescence detection was performed at 230 nm excitation and 320 nm emission [validation: limit of detection 50 nmol·l^{-1}, precision $<8\%$, accuracy $< \pm 8\%$ (data on file, Nycomed)]. Morphine and its metabolites were analysed by a method using electrochemical detection. One millilitre of plasma was prepared with 0.1 ml of the internal standard solution (containing 100 pmol HN-52076) and 1 ml of 0.5 M ammonium sulphate buffer (pH = 9.3). A volume of 2 ml was loaded onto Seppak light SPE C18 columns and washed with conditioning buffer. A sample of 0.2 ml of the eluted solution was analysed using an HPLC system consisting of autosampler, pump and UV detection (all from the HP 1050 series), column oven (BFO 04) and an electrochemical detector (ESA Coulochem II). Separation was achieved on a Hypersil BDS C8 column. Morphine, M6G and the internal standard were detected by electrochemical detection at 350 mV [validation: limit of detection 2 nmol·l^{-1}, precision $<8\%$ and accuracy $< \pm 2\%$ (morphine) and $< \pm 14\%$ (M6G) (data on file, Nycomed)] and M3G by UV detection at 214 nm (validation: limit of detection 25 nmol·l^{-1}, precision $<16\%$, accuracy $< \pm 7\%$).

Comparisons between groups were done with the Mann-Whitney test and comparison of frequencies with Fisher's exact test. Relations between different variables were evaluated with the Spearman rank correlation test.

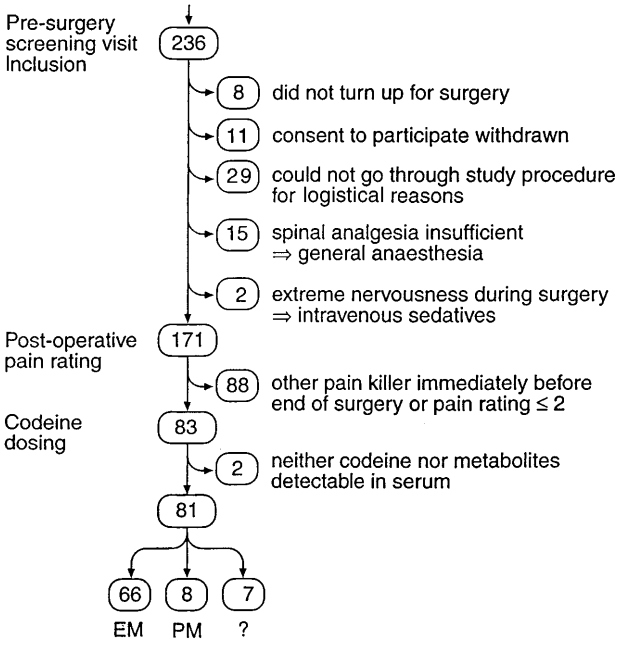

Fig. 1 Patient flow through the study phases

Results

In two patients neither codeine nor any of its metabolites could be detected in serum. These patients were excluded from further data analysis, since it had to be assumed that they did not receive codeine. Urine samples from seven patients were lost. Of the remaining 74 patients, 8 were poor metabolizers and 66 were extensive metabolizers of sparteine. Clinical data on these 81 patients are given in Table 1. The codeine serum concentrations ranged from below the limit of determination of the assay 50 nmol·l^{-1} to 780 nmol·l^{-1}. The serum concentrations of morphine and M6G 1 h after codeine are shown in Fig. 2. In 22 patients, including the eight poor metabolizers, the serum concentrations of both morphine and M6G were below the limit of determination of the assay, i.e. 1.5 nmol·l^{-1}and 2 nmol·l^{-1} respectively (Figs. 1 and 2). A sum of the concentrations of these two substances below 10 nmol·l^{-1} was found in an additional eight patients. There was no correlation between age and the sum of the serum concentration of morphine plus its 6-glucuronide ($R_S = -0.12$, $P = 0.25$) and no

Table 1 Clinical data for patients completing the study

	Total	Morphine plus morphine-6-glucuronide serum concentration	
		< 10 nmol·l^{-1}	≥ 10 nmol·l^{-1}
Number	81	30	51
Male/female	54/27	19/11	35/16
Age[a]	52 (20–84)	52 (20–83)	51 (20–84)
Sparteine phenotype			
EM/PM/unknown[b]	66/8/7	20/8/2	46/0/5
Operation			
Varicose veins/hernia/other	50/26/5	17/11/2	33/15/3

[a] Median (range)
[b] *EM* extensive metabolizer, *PM* poor metabolizer

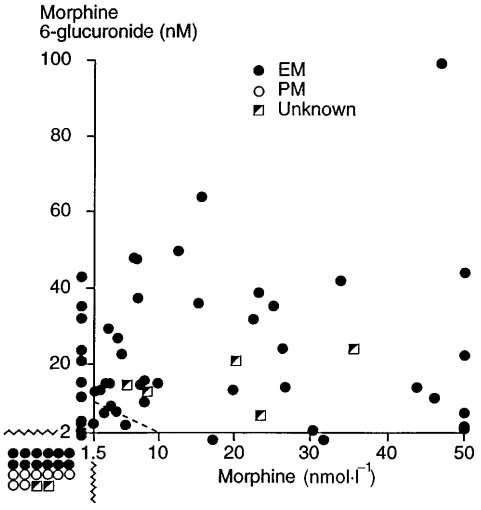

Fig. 2 Serum concentrations of morphine and morphine-6-glucuronide 1 hour after oral administration of 100 mg codeine. Axes crossed at the limit of determination for the assay (1.5 nmol·l^{-1} for morphine and 2 nmol·l^{-1} for morphine-6-glucuronide). (●) extensive and (○) poor metabolizers of sparteine, (◩) undetermined phenotype

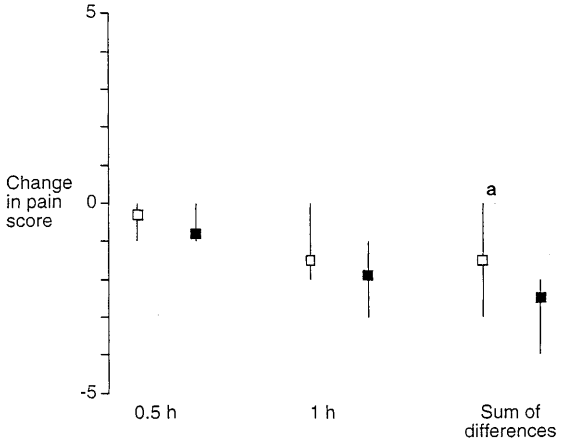

Fig. 3 Change in post-operative pain score 0.5 h and 1 h after oral administration of 100 mg codeine, and the sum of these differences for patients with serum concentrations of morphine plus morphine-6-glucuronide below (□) and over (■) 10 nmol·l^{-1}. Medians with 95% confidence intervals are given. a: $P = 0.058$

difference in frequency of subjects with concentrations of active metabolites below the level of determination between male and female patients (15/54 vs 7/27, $P = 1$).

The median pre-medication pain rating was 4.4 (range 3–10). Thirty-eight per cent of the patients had received escape medication at some time during the first 2 h after codeine intake and this figure increased to 41% when the entire observation period of 4 h was taken into account. This would be expected to interfere with the efficacy evaluation for codeine, and therefore only data from the first hour after medication was included in the analysis of analgesic effect, since only 16% had received escape medication within this time period. None of these were poor metabolizers ($P = 0.25$). There was no difference in the sum of pre- minus post-medication pain rating differences between extensive and poor metabolizers of sparteine (median 2.2 vs 3.0, $P = 0.60$). The pre- minus post-medication pain rating differences at 0.5 h and 1 h after codeine and the sum of these differences for patients with serum concentrations of morphine plus M6G of < 10 nmol·l^{-1} and > 10 nmol·l^{-1} are shown in Fig. 3. There was a marginally significant difference in the sum of differences between these two groups of patients (median 1.5 vs 2.5, $P = 0.058$). There was no correlation between the serum concentration of morphine plus M6G and the sum of differences in preminus post-medication pain ratings ($R_S = 0.12$, $P = 0.25$).

Discussion

The serum concentrations of morphine and its metabolites found 1 h after codeine in extensive metabolizers in the present study were unexpectedly low in comparison with previous studies with healthy volunteers (Quiding et al. 1986; Sindrup et al. 1990; Yue et al. 1991; Sindrup et al. 1992; Desmeules et al. 1991). Thus, in one study we found plasma concentrations of morphine from 4 to 62 nmol·l^{-1} (median 12 nmol·l^{-1}) 1 h after an oral dose of 100 mg codeine in extensive metabolizers of sparteine. The most likely explanation for the present finding is delayed absorption due to surgical stress.

In line with the studies in healthy volunteers (Sindrup et al. 1990; Desmeules et al. 1991; Yue et al. 1991), we

also found that in poor metabolizers morphine and its metabolites cannot be detected after codeine intake.

Codeine appears from this study to be a weak post-operative analgesic, with 41% of the patients requiring escape medication within 4 h of codeine administration. Further, the reduction in pain score during the post-operative observation period may not have been significantly different from the reduction seen with no treatment, i.e. a spontaneous reduction in pain with time after surgery. The low efficacy of single doses of codeine has also been observed by others (Jochimsen and Noyes 1978; Honig and Murray 1984; Quiding et al. 1993).

With the overall low efficacy of codeine observed in the present study, it is very difficult to detect subgroup differences in effect. Bearing this in mind, together with the fact that the number of poor metabolizers was small ($n = 8$), it is not surprising that there was no statistically significant difference in analgesic effect between extensive and poor metabolizers. Further, many of the extensive metabolizers did not, like the poor metabolizers, have any detectable amount of morphine or its metabolites in their serum. However, the hypothesis of codeine analgesia through metabolically formed morphine was supported by the finding that the patients with concentrations of morphine plus M6G over 10 $nmol \cdot l^{-1}$ had a significantly better response than patients with a concentration of these substances below this level. In a previous study including 25 patients following oral surgery and a design fairly similar to ours, there appeared not to be any difference between the analgesic effect for the four patients with non-detectable plasma concentrations of morphine and the remainder (Quiding et al. 1993). This finding may have been spurious due to the low number of patients without detectable levels of morphine. In a recent patient-controlled analgesia study with codeine for post-operative pain in ten extensive metabolizers and one poor metabolizer, it was found that codeine was ineffective in the poor metabolizer and one of the extensive metabolizers (Persson et al. 1995). Further studies on the impact of CYP2D6 status on post-operative pain relief with codeine are needed, preferably with larger patient groups. It appears that designs with either multiple-dose or patient-controlled analgesia may be necessary.

It is concluded that after single oral doses of codeine in patients with post-operative pain, the plasma concentrations of morphine and its metabolites are very low, and pain relief is insufficient in many patients. In poor metabolizers, morphine in plasma was below the level of determination, but this was also the case for some extensive metabolizers, and in this phenotype, a substantial number of patients had very low levels of morphine and its metabolites. In all patients with low or non-determinable levels (extensive and poor metabolizers), pain relief was less than in patients with higher levels, but probably due to the small number of poor metabolizers, there was no significant difference between the two phenotypes.

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