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Patient-controlled analgesia (PCA) with codeine for postoperative pain relief in ten extensive metabolisers and one poor metaboliser of dextromethorphan

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Postoperative pain relief with codeine was evaluated in 11 women undergoing hysterectomy. Patient-controlled analgesia (PCA) was used to administer codeine. After the study the patients were phenotyped with respect to the *O*-demethylation of dextromethorphan (cytochrome P4502D6 polymorphism). Ten were extensive metabolisers and one a poor metaboliser. There was a nine-fold variation in the minimum plasma concentration of codeine consistent with pain relief (40–350 ng ml^{-1}). Two patients did not experience any effect of codeine, one of whom was a poor metaboliser of dextromethorphan, confirmed by genotyping. In the other nine patients the effective dose of codeine varied from 4.8–25.3 mg h^{-1}.

Keywords analgesic effect codeine cytochrome P4502D6 morphine intravenous administration PCA genetic polymorphism

Introduction

Codeine is *O*-demethylated to morphine by cytochrome P4502D6 which has a monogenic pattern of inheritance. The activity of this metabolic pathway co-segregates with the sparteine/debrisoquine/dextromethorphan oxidative polymorphism [1–3]. In *experimental* pain models a lack of analgesic effect of codeine in the poor metaboliser (PM) phenotype was attributed to lack of formation of morphine [4]. The present *clinical* study attempted to define the kinetics and efficacy of codeine in postoperative pain relief, with preliminary observations on the role of CYP2D6 phenotype.

Methods

The study protocol was approved by the local Ethics Committee.

Subjects

Eleven women admitted to hospital for hysterectomy, mean age 47 years (range 37–66 years),were included in the study. Their mean body weight was 72 kg (range 57–99 kg). All gave their informed consent for participation. Patients with liver/kidney insufficiency, allergic disposition, chronic respiratory disease, diseases of the gall bladder, abuse or recent consumption of codeine or any other drugs were excluded. The results of standard blood chemistry tests (haemoglobin, haematocrit and serum concentrations of bilirubin, alkaline phosphatase, liver transaminases, sodium, potassium and creatinine) were within normal ranges.

Anaesthesia

All patients were premedicated with an oral dose of 10 mg diazepam 1–2 h before induction of anaesthesia. Atropine (0.5 mg) was given intravenously immediately before induction. Anaestheia was induced with droperidol 2.5 mg, midazolam 1–2 mg, fentanyl citrate 0.1 mg and thiopentone 2–3 mg kg^{-1}. Orotracheal intubation was performed after administration of vecuronium (0.1 mg kg^{-1}). Anaesthesia was maintained with nitrous oxide and oxygen (70:30). In addition, vecuronium, fentanyl citrate, 0.05–0.1 mg,

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and midazolam, 1–2 mg, were given as needed. Muscle relaxation was reversed postoperatively. After tracheal extubation, the patients were transferred to a recovery room where they remained overnight. Respiratory rate, heart rate and blood pressure were checked at least hourly. Intravenous fluid and blood transfusions were given as required.

Assessment of pain

Pain was assessed with a visual analogue scale (VAS) consisting of a 10 cm horizontal line marked 'No pain' at its left end and 'Worst imaginable pain' at its right end.

Pain was assessed before the start of PCA at 1, 2 and 4 h and then every 4 h thereafter. The patients were not shown their previous scores.

Pain relief was presented as percent reduction of pain from:

$$\frac{\text{VAS before} - \text{VAS during}}{\text{VAS before}} \times 100$$

PCA

The PCA-pump (Prominject, Pharmacia, Sweden) was programmed to deliver fixed i.v. doses of codeine phosphate (10 mg, corresponding to 21 μmol of codeine) with a minimum time interval of 5 min between doses. If the patient needed more analgesic she was classified as a drop-out. The PCA-pump was filled with codeine phosphate solution (20 mg ml^{-1}) and was first used when the patient asked for pain relief for the first time after surgery. PCA was commenced in the afternoon after surgery. No other analgesics were administered during PCA. The hourly consumption of codeine during PCA was recorded as were the time intervals between doses. The PCA was continued until 07.00 h the following morning when the patients were given conventional analgesics if needed.

Blood sampling

Venous blood samples (5 ml) were collected during PCA for drug assay. The first sample was collected before PCA administration started followed by samples at 1, 2, 3 and 4 h after the first intravenous dose of codeine. Blood samples were also collected before and at 15, 30, 45, 60, 90, 120, 240 and 360 min after the pump was disconnected from the patient. The samples were centrifuged immediately and the plasma separated and frozen at −20° C until assay. Concentrations of codeine and its metabolites norcodeine, morphine, morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G) and codeine-6-glucuronide (C6G) were assayed by h.p.l.c. [5–6]. Limits of detection and intra-assay coefficient of variation were: codeine (1 ng ml^{-1}; 3% at 25 ng ml^{-1}); norcodeine (1 ng ml^{-1}; 8% at 5 ng ml^{-1}); morphine (1 ng ml^{-1}; 10% at 2 ng ml^{-1}); M3G (9 ng ml^{-1}; 7% at 9 ng ml^{-1}); M6G (0.2 ng ml^{-1}; 7% at 2 ng ml^{-1}); C6G (10 ng ml^{-1}; 20% at 25 ng ml^{-1}).

Phenotyping and genotyping

On the third day after surgery (after an overnight fast) each patient was given one 30 mg capsule of dextromethorphan (Tussidyl®, TIKA, Sweden) and a venous blood sample was collected 3–4 h later. Serum was isolated and frozen at −20° C. Dextromethorphan and its *O*-demethylated metabolite dextrorphan were measured and the dextromethorphan/dextrorphan ratio was used as an assessment of the CYP2D6 phenotype [7]. In addition, patients 1 and 10 were genotyped with respect to the CYP2D6 polymorphism according to Smith *et al.* [8].

Pharmacokinetics

Intravenous data from a previous study [9] were fitted by a two-compartment model using the NONMEM (Non Linear Mixed Effects Model) program [10]. The choice of model was based on visual inspection of the concentration *vs* time plots. Hence population mean values of the pharmacokinetic parameters and estimates of their variability were obtained. The population and variances were then used in conjunction with the sparse plasma concentration data from the current study in a Bayesian estimation procedure [14].

Results

The clinical course of the eleven patients was uncomplicated. None reported any severe adverse reactions although some felt sick postoperatively, an effect which may have been a consequence of the anaesthetic.

The patient's phenotypes with respect to CYP2D6 activity are shown in Table 1. The phenotypes of patients 1 and 10 were confirmed by genotyping for the cytochrome P4502D6 enzyme. Nine of the eleven patients experienced satisfactory pain relief, defined as no need of additional analgesia. The average codeine dose in this group was 12.6 ± 6.6 mg h^{-1} (range 4.8–25.3 mg h^{-1}).

Patient 5 requested additional analgesia as her codeine self-administration was not sufficient. This patient had severe hip damage which probably accounted for the need for more potent analgesia. Patient 10, a PM, was also a drop-out and withdrew after 1.4 h because of a lack of effect of codeine. Her total codeine consumption was 103.6 mg h^{-1} (Table 1). She received ketobemidone as default medication.

The time interval between the last dose of fentanyl during anaesthesia and the first VAS score was 2.3 ± 0.8 h. The fentanyl dose requirement was 0.5 ± 0.1 mg.

Pain assessment on the VAS scale averaged 57 ± 19 mm (distance from the 'no pain' end of scale) in the EMs before start of PCA. At the end of the PCA period the pain relief was 73 ± 14%. Maximum recorded pain relief was 85 ± 12% (Table 1). Patient 10 consumed 4–20 times more codeine than the other patients in just 1.4 h. She indicated a worsening

Table 1 Dosage, plasma drug concentrations and analgesic response to PCA with codeine

Patient	Metabolic ratio	CL (ml min^{-1} kg^{-1})	C_{m3g} (ng ml^{-1})	C_{m6g} (ng ml^{-1})	C_m (ng ml^{-1})	C_{ncn} (ng ml^{-1})	C_{c6g} (ng ml^{-1})	C_{cod} (ng ml^{-1})	Total codeine dose (mg)	Average time between doses (min)	Duration of PCA (h)	Pain before PCA (mm)	Reduction of initial pain (%) Maximum	Reduction of initial pain (%) At end of PCA
1	0.51[f]	7.6	—	4.0	7.2	24	325	278	150	62 (50)	15.8	50[a]	60	60
2	0.04[f]	9.8	76.3	5.6	1.7	145	570	88	60	48 (17)	4.8	86	86	79
3	0.06[f]	11.0	—	—	—	91	275	87	30	124 (32)	6.2	48	79	79
4	0[f]	7.8	177	6.8	—	9	907	268	240	38 (20)	15.1	72	96	65
5[b]	0.01[f]	9.6	134	20.9	29.5	45	1962	578	165	27 (27)	4.1	50	30	30
6	0.01[f]	7.5	42.6	8.2	8.7	33	430	158	90	93 (89)	14.0	50	90	80
7	0.02[f]	—	50.5	11.0	47.5	9	790	407	400	22[c]	15.8	50	80	70
8	0.01[f]	9.8	—	—	—	42	901	308	110	92 (159)	16.9	80	94	94
9	0.02[f]	11.0	—	87.5	22.5	15	1232	585	280	40 (44)	18.6	50	100	46
10[b]	2.00[g]	7.0	22	4.7	5.3	31	2110	617	145	7 (1)	1.4[c]	75		−30
11	0[f]	9.7	50	3.5	2.1	33	508	133	250	34 (18)	14.0	25	80	80
Mean		9.1	78.9	16.9	15.6	43	950	319	179[d]	66[e]	13.4[d]	57[d]	85[d]	73[d]
(s.d.)		(1.5)	(n = 7) (56.1)	(n = 9) (27.0)	(n = 8) (16.3)	(41)	(645)	(202)	(121)	(33)	(4.7)	(19)	(12)	(14)

[a]Distance from the 'no pain' end of the 100 mm visual analogue scale. [b]Drop-out. Patient 10 was a poor metaboliser of dextromethorphan, PM. [c]The s.d. could not be estimated due to technical error. [d]n = 9. Patients 5 and 10 are excluded. [e]n = 8. Patients 5, 7 and 10 are excluded.
[f]Extensive metaboliser of dextromethorphan, EM. The phenotype of patient no 1 was confirmed with debrisoquine. [g]Poor metaboliser of dextromethorphan, PM.
C refers to concentration of codeine metabolite 2-4 h after the final dose of codeine.

of pain during this period (VAS −30%, Table 1, Figure 1).

All patients received codeine in a consistent way, with an almost constant input per hour after the first few hours. The mean time interval between doses ranged from 27 to 124 min per individual and the need for codeine (total amount) ranged from 30–400 mg in the EMs. The corresponding values in the poor metaboliser were 7 min and 145 mg.

Calculated and observed plasma codeine concentrations in four patients are shown in Figure 1. A pseudo steady-state concentration was achieved which tended to be maintained throughout the PCA in most patients with satisfactory pain relief. No significant tendency was observed either for codeine consumption or its plasma concentrations to increase with time.

The pharmacokinetic parameters of codeine and plasma concentrations of codeine and its main metabolites are shown for each patient in Table 1.

The kinetics of codeine were similar in those patients (5 and 10) who experienced unsatisfactory effect to those in the rest of the patients. Compared with the average patient, patient 5 had high and patient 10 medium concentrations of morphine and M6G. These individuals had the highest plasma concentrations of C6G.

Discussion

All patients but two experienced satisfactory pain relief from the treatment with codeine by PCA. Although concern has been expressed about the risk of histamine-release and vasodilatation after intravenous administration of codeine [11], none of these problems was observed in our patients.

Pain was assessed in each patient when she required codeine PCA postoperatively on the first occasion. Therefore, any difference in fentanyl dose requirement during anaesthesia should not influence the results.

Our data show that the PCA with codeine was satisfactory in most patients and that large interindividual variation in plasma drug concentrations were associated with satisfactory pain relief. However, two patients had insufficient or no effect of codeine. According to protocol these patients were classified as drop-outs as they needed additional medication. Patient 5 had severe hip damage which required more potent analgesia. Patient 10 was a poor metaboliser of dextromethorphan and hence a low rate of morphine formation might be expected to have contributed to therapeutic failure. However, this patient had medium to high plasma concentrations of morphine and M6G compared with the other individuals. Possibly, local formation of morphine from codeine in the central nervous system may have been sufficiently impaired in the PM to decrease the pain relieving effect of codeine? Although our findings are consistent with the theory that CYP2D6 plays an important role in codeine analgesia, this issue clearly requires further investigation.

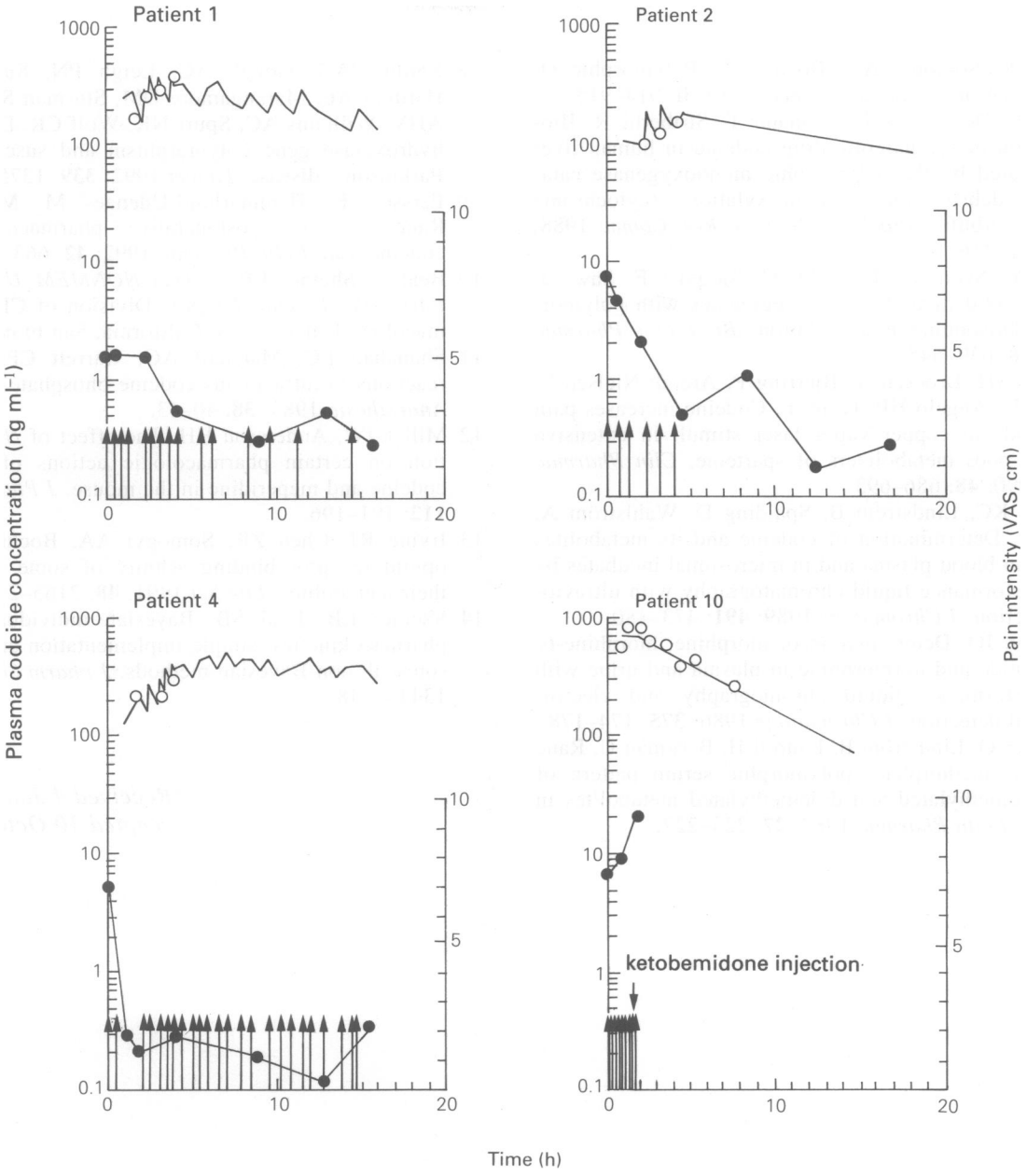

Figure 1 Plasma concentrations of codeine (○) and pain intensity (●) during PCA in four patients. The continuous lines for plasma concentrations are computer-calculated values. ↑ indicates application of PCA.

There is no evidence to date that metabolites of codeine other than morphine and M6G produce an analgesic effect. In animals, there is no significant analgesic effect from norcodeine [12]. As far as we know, C6G has not been shown to have any analgesic effect. Consistent with this, the binding affinity of C6G to the μ-opioid receptor in rat brain homogenate is 300 times less than that of morphine and M6G, but similar to that of codeine [13]. Thus, it is unlikely that C6G contributes to analgesia and/or toxicity, even though its plasma concentrations are about 10–15 times higher than those of codeine [9]. Our results in patient 10, who experienced unsatisfactory pain relief, yet had the highest C6G concentration of all patients, are in support of this view.

In summary, our study has demonstrated the utility of codeine alone for the treatment of pain after hysterectomy by PCA. However, the study did not reveal any significant correlation between plasma concentrations of the metabolites of codeine and its pain relieving effect. The data obtained in the single PM emphasize the need for further studies of the role of cytochrome P4502D6 and morphine generated from codeine in the effect of codeine when used to treat postoperative pain.

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