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CASE REPORT

NORPETHIDINE TOXICITY AND PATIENT CONTROLLED ANALGESIA

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SUMMARY

Patient-controlled analgesia (PCA) with i.v. opioids is prescribed increasingly. We report three cases of norpethidine toxicity in patients receiving pethidine by PCA. (Br. J. Anaesth. 1993; **71**: 738–740)

KEY WORDS

Analgesia: patient-controlled. Opioids: pethidine. Complications: norpethidine toxicity.

CASE REPORTS

Patient No. 1

A 61-yr-old, 54-kg female was admitted for closure of ileostomy, 4 months after a right-hemicolectomy for angiodysplasia. She had a history of chronic obstructive airways disease and chronic hip pain. There was no history of convulsions. Her long-term drug therapy comprised theophylline, salbutamol, inhaled steroids, amitriptyline, carbamazepine, frusemide and somatostatin. The carbamazepine was prescribed for her chronic hip pain. She said that she wheezed if given morphine. Eleven days after closure of the ileostomy, she required a laparotomy and repeat ileostomy for an anastomotic leak.

Extradural pethidine was used for analgesia for 4 days after the closure of ileostomy, followed by intermittent i.m. pethidine. After the laparotomy, i.v. pethidine by PCA was commenced.

The day after the laparotomy, the patient was noted to be anxious and to have a tremor, and she had an episode of rhythmic twitching. She was treated with i.v. diazepam 3 mg. At 36 h after starting PCA, she received clonazepam 0.5 mg i.v. for further twitching and at 48 h she had tonic clonic spasms affecting the legs more than the arms. Each episode lasted for about 1 min, with associated cyanosis, and eventually she had a grand mal seizure. The airway was maintained, oxygen therapy was continued and additional clonazepam 2 mg i.v. was given in increments. Pethidine was discontinued and carbamazepine, which had been omitted for the previous 4 days, was recommenced. The patient was transferred to the Intensive Care Unit. No further grand mal seizures occurred, but twitching and muscle spasms were noted for another 5 days. The patient made a full neurological recovery.

During the 9 days preceding laparotomy, she had received pethidine up to 375 mg day^{-1}. After the laparotomy, she was given pethidine PCA with 10-mg boluses but no background infusion. Because of lack of pain control, boluses were increased to 20 mg on the first day after operation. The patient had self-administered pethidine 1760 mg and 1540 mg in the first and second 24-h periods, respectively.

The blood concentration of norpethidine on the day after the convulsion was 1.55 μg ml^{-1}.

On the day of the convulsion, serum potassium concentration was 2.6 mmol $litre^{-1}$ and creatinine concentration 0.12 μmol $litre^{-1}$. Serum ionized calcium was normal, blood glucose was 13.5 mmol $litre^{-1}$ and serum concentration of theophylline was not in the toxic range. Arterial blood–gas tensions with oxygen therapy via a face mask immediately after treatment of the convulsion were P_{O_2} 8 kPa, P_{CO_2} 8 kPa and pH 7.24. This respiratory acidosis and relative hypoxia resolved with oxygen therapy and spontaneous ventilation.

Patient No. 2

A 21-yr-old, 51-kg female was admitted for an abdomino–perineal resection of the rectum for Crohn's disease. She was suspected of opioid abuse. On admission to hospital, she reported that she had not taken pethidine recently. There was no history of convulsions. Her drug therapy was oral prednisolone, azathiaprine and metronidazole. She claimed to have a morphine "allergy", which caused hallucinations.

She received pethidine 200–400 mg i.m. for perineal inflammatory pain daily for 5 days before operation. After operation, i.v. pethidine by PCA was commenced, with 10-mg boluses and 10 mg h^{-1} by background infusion. The bolus size was increased to 20 mg 12 h later, as analgesia was considered to be uncontrolled. On the second day after operation, the patient had myoclonic jerks and felt frightened. She had used an average of pethidine 1240 mg/24 h. Norpethidine toxicity was suspected, pethidine was discontinued and morphine commenced by PCA. The myoclonic twitching abated with this regimen.

This patient's blood norpethidine and pethidine concentrations shortly after ceasing pethidine were

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TABLE I. *Pethidine doses used by the three patients receiving PCA*

	Patient 1	Patient 2	Patient 3
1st 24 h (mg)	1760	1200	1200
Next 20.5 h (mg) or 2nd 24 h (mg)	1540	1100	1280
Next 2 h (mg) or 4 h (mg)	200		280
Average dose in 24 h (mg)	1344	1240	1274
(mg/kg b. wt)	24.9	24.3	24.0

TABLE II. *Doses of pethidine received during 24 h on PCA, timing of blood samples after stopping pethidine and blood concentrations of norpethidine (Norpeth.) and pethidine (Peth.) where available*

	Pethidine (mg)			Blood concn ($\mu g\ ml^{-1}$)	
Patient No.	Before PCA	Average/24 h PCA	Time to sample (h)	Norpeth.	Peth.
1	1900 in 9 days	1680	18	1.55	—
2	1700 in 5 days	1240	1	3.2	1.7
3	0	1274	1	1.67	2.4

3.2 and 1.7 $\mu g\ ml^{-1}$, respectively. Serum urea, electrolytes, creatinine and blood glucose concentrations were normal.

Patient No. 3

A 31-yr-old, 53-kg female with a 4-yr history of Crohn's disease was admitted to hospital with small bowel obstruction. Four days later, she required laparotomy and right hemicolectomy. Before admission, loperamide was her only drug therapy. No pethidine was given before operation.

After operation, the patient was given i.v. pethidine by PCA. Bolus doses were increased from 10 mg to 20 mg because of lack of pain control after 2.5 h. There was no background infusion.

On the first day after operation, she was noted to be anxious and to have a strange affect. She had consistently reported high pain scores, despite having used pethidine 1200 mg in 24 h. She did not feel tremorous and had no involuntary movements. PCA pethidine was continued and on the second day after operation she seemed more agitated and reported that she felt frightened. She had used pethidine 1280 mg in the second 24 h. The pain scoring had remained high.

Pethidine was stopped and morphine PCA started. The patient received three 5-mg i.v. doses of diazepam over the next 24 h. She felt less frightened and her pain scores improved. She used morphine 106 mg over the next 24-h period.

The blood norpethidine and pethidine concentrations were 1.67 and 2.4 $\mu g\ ml^{-1}$, respectively, shortly after cessation of pethidine. Serum urea, electrolytes, creatinine and blood glucose concentrations were normal.

Pethidine dosage and blood concentrations

The amounts of pethidine used by these three patients while receiving PCA, including their average 24-h dosage, are shown in table I. The amount of pethidine administered to each patient, the time between stopping pethidine and sampling for blood concentrations and the blood concentrations of norpethidine (and pethidine where available) are summarized in table II.

DISCUSSION

Pethidine is metabolized by two hepatic pathways, hydrolysis and N-demethylation, to pethidinic acid and norphethidine, respectively. Norpethidine is hydrolysed similarly to an acidic form. Urinary excretion is the principal elimination route. The elimination half-life of pethidine is 3–6 h, whilst that of norpethidine is at least 15 h, and up to 35 h in patients with renal failure [1, 2].

Norpethidine has CNS excitatory effects in animals and there is evidence [3] of increasing intensity of CNS excitation correlating with accumulation of norpethidine in plasma in human subjects receiving pethidine. The excitatory effects range from mild nervousness through tremors, twitches and multifocal myoclonus to seizures.

Norpethidine toxicity has been described well in various clinical situations [3–10]. Reduced renal function has been noted to predispose to accumulation of norpethidine [1, 11]. Goetting, Thirman and Arbor [5] described norpethidine neurotoxicity in a patient self-administering oral pethidine after operation. Oral pethidine predisposes to norpethidine toxicity because of extensive first-pass hepatic metabolism.

These are the first reported cases of norpethidine toxicity in association with parenteral PCA pethidine. In our first two patients there had been some administration of pethidine before starting PCA. This would have provided an opportunity for both cumulation of norpethidine before operation and the development of tolerance to the analgesic effect of pethidine. The latter would predispose to an early increased use of PCA pethidine for analgesia. In addition, some enzyme induction from previous drug administration could have predisposed to N-demethylation. In the third patient, the only preoperative drug therapy was loperamide. Loperamide, a piperidine derivative, is a congener of pethidine and its metabolism in the rat includes oxidative-N-demethylation [12]. Oral loperamide is partly excreted unchanged in the faeces (25–40 % in man) and it does not exert opioid activity in normal therapeutic doses [13]. We suggest that there may have been potential for induction of N-demethylation enzymes related to chronic administration of loperamide in our third patient. This could have predisposed to the development of norpethidine toxicity with PCA pethidine.

The blood concentrations of norpethidine (assayed by a chromatographic method) in our patients (table I) were within and greater than the ranges of plasma concentrations of norpethidine associated with CNS excitation observed by Kaiko and colleagues [3]. Edwards and colleagues [11] found in several studies that blood and plasma concentrations of pethidine are comparable and therefore it seems reasonable to compare our results from blood with plasma concentrations described elsewhere. For the two patients in

whom the blood norpethidine:pethidine ratio was available, it was within the ranges associated with evidence of CNS excitation in the study by Kaiko's group [3].

Previous case reports have suggested that, if long-term or high-dose opioid analgesia is anticipated, especially in the presence of renal impairment, the use of pethidine may carry an appreciable risk of norpethidine toxicity. We suggest that use of pethidine immediately before surgery may also predispose to increased risk of developing norpethidine toxicity if pethidine is to be used after operation. This risk is increased in a situation in which the patient may receive large doses of pethidine, as with PCA. In all three patients, analgesia was poor and this exacerbated the tendency to administer more pethidine.

Any patient receiving pethidine in repeat doses should be monitored for early signs of norpethidine toxicity. If norpethidine toxicity is suspected, pethidine should be ceased, and ventilatory support and anticonvulsant therapy given if indicated. Naloxone does not reverse norpethidine toxicity and may worsen the situation by its antagonistic effect on the CNS-depressant effect of pethidine [14]. Morphine is usually a suitable substitute analgesic as it lacks a major excitatory metabolite such as norpethidine. However, it should be noted that morphine may exhibit some neuroexcitatory effects in very large doses [2, 15].

All three of our patients were using pethidine in excess of 1200 mg/24 h on PCA, equivalent to 24–25 mg kg^{-1}/24 h. The results of a recent study of norpethidine toxicity in sickle cell crisis [10] suggested that daily doses of parenteral pethidine exceeding 25 mg kg^{-1} may be associated with toxicity, especially in the presence of renal impairment or if pethidine had been taken orally before hospital admission.

Our first patient had appeared to be anxious and patients Nos 2 and 3 had volunteered that they felt frightened, in association with the use of more than 1200 mg of pethidine in 24 h and apparent poor quality of analgesia. The presence of anxiety in patients receiving large doses of pethidine without the expected analgesic response should alert to the possibility of norpethidine toxicity.

Approximately 10 % of the 1500 patients each year who use postoperative PCA within the Acute Pain Service at the Royal Adelaide Hospital are prescribed pethidine. Morphine is the preferred drug. Those receiving pethidine usually do so because of a history of morphine allergy or a stated preference by the patient in light of previous experience. The majority of patients who have been given PCA pethidine experienced no problems. Our three patients presented in the same hospital over a 2-year period and are presented in chronological order.

Our patients demonstrate that, although PCA is generally considered to be safe in terms of ventilatory and sedative side effects in healthy patients, this complication of metabolite toxicity can develop. In addition to monitoring ventilation and state of sedation, frequent clinical assessment and recording the amount of drug used is required to minimize such risks.

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