Respiratory depression following combination of epidural buprenorphine and intramuscular ketorolac

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Summary

A 48-year-old man who had undergone thoracotomy for carcinoma of the middle third of his oesophagus developed severe postoperative respiratory depression following intramuscular ketorolac 30 mg 2 h after 150 μg epidural buprenorphine. Summation of analgesia by drugs used in combination can have deleterious respiratory effects.

Key words

Anaesthetic techniques, regional; epidural. Analgesics; buprenorphine, ketorolac. Complications; respiratory depression.

Combinations of analgesics are commonly used to provide optimum pain relief with minimal side effects. Different types of drugs may be used together and various routes of administration may be employed. Low-dose epidural opioid combined with intramuscular nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to provide good postoperative pain relief [1]. Although one of the aims of combined therapy is to decrease the dose of epidural opioid required, care should be taken to ensure that the therapeutic index of the combination is adequately assessed. This case report describes severe, unexpected respiratory depression after a combination of intramuscular ketorolac and epidural buprenorphine for postoperative pain relief.

Case history

A 48-year-old man with carcinoma of the middle third of his oesophagus underwent total oesophagectomy under general anaesthesia. This involved a right sided thoracotomy and upper midline laparotomy with colonic anastomosis in the neck. The patient had had no previous general anaesthetics and both the past medical and family histories were unremarkable. He was not receiving any medication and had no known drug allergies.

The patient received diazepam 10 mg intramuscularly 30 min before surgery. Anaesthesia was induced with thiopentone (5 mg.kg⁻¹) and following suxamethonium (1.5 mg.kg⁻¹), the patient's trachea was intubated with an 8.5 mm oral cuffed tube. Anaesthesia was maintained with O₂ 30%, N₂O 70%, halothane 0.5%, pentazocine 0.6 mg.kg⁻¹ and pancuronium 0.06 mg.kg⁻¹ using controlled ventilation and a circle absorber. The electrocardiograph (ECG), pulse, arterial blood pressure, end-tidal CO₂ and peripheral oxygen saturation were monitored intra-operatively. A central venous cannula (CVP) was inserted through an antecubital vein. The patient was haemodynamically stable throughout the operation with a blood loss of 600 ml, which was replaced with 450 ml whole blood. The operation lasted 5 h, during which time the patient also received 2.5 l lactated Ringer’s solution and 500 ml 5% dextrose in water. Before reversal, using a lateral approach an 18 G epidural catheter was introduced at T₁₀ using the loss of resistance method. Residual neuromuscular blockade was reversed with neostigmine (0.05 mg.kg⁻¹) and atropine (0.025 mg.kg⁻¹) and satisfactory recovery confirmed with train-of-four stimulation using a peripheral nerve stimulator.

After reversal the patient was conscious, obeying commands and able to maintain a clear airway. His pulse rate was 84 beat.min⁻¹ and arterial blood pressure 130/80 mmHg. One hour later, after transfer to the recovery ward, he complained of severe pain at the operative site. Epidural buprenorphine 150 μg (3 μg.kg⁻¹) diluted in 10 ml normal saline was given after careful aspiration to exclude aberrant placement of the catheter and this took effect after 30 min. Oxygen was given with nasal prongs at a flow of 4 l.min⁻¹. As judged clinically, the
patient's tidal volume was satisfactory and his respiratory rate was 16 breath.min⁻¹. Arterial blood gas analysis showed pH 7.25, \(P_O_2\) 16.3 kPa, \(P_CO_2\) 5.9 kPa, base excess -7.7, standard bicarbonate 19.2 m.mol.l⁻¹ and oxygen saturation 98%. Metabolic acidosis was corrected with 50 ml 8.5% sodium bicarbonate. At this stage the patient's core temperature was 35°C.

Two hours after the epidural buprenorphine the patient again requested analgesia as he was still experiencing pain. It was considered inadvisable to give a further supplemental dose of epidural buprenorphine, and ketorolac 30 mg (0.6 mg.kg⁻¹) was given intramuscularly. During the next hour the patient became drowsy, stopped obeying commands and developed bradypnoea (6 breath.min⁻¹). However, his pulse and arterial blood pressure remained stable. Immediate arterial blood gas analysis showed pH 7.22, \(P_O_2\) 8.6 kPa, \(P_CO_2\) 18.4 kPa, base excess -2.6, standard bicarbonate 26.7 m.mol.l⁻¹ and \(O_2\) saturation 99%. The chest was clear on auscultation and there was no evidence of any respiratory obstruction. The patient's trachea was reintubated and intermittent positive pressure ventilation was instituted. A chest X ray performed immediately was clear and both plasma glucose and electrolyte values were within their normal ranges. Doxapram was unavailable.

After 6 h mechanical ventilation the patient became alert and was able to make good respiratory efforts. Ventilation was discontinued; the patient was allowed to breathe oxygen-enriched air through a T-piece system. He maintained satisfactory ventilation as indicated by blood gas analysis and his trachea was extubated 1 h later. The epidural catheter was removed the next day.

Discussion

This case describes an instance of respiratory depression following intramuscular ketorolac (30 mg) given as a supplement after epidural buprenorphine (150 \(\mu\)g). Adequate pain relief did not occur even 2 h after epidural buprenorphine, while severe respiratory depression developed within 1 h of ketorolac administration. Respiratory depression after epidural buprenorphine may occur in cases of inadvertent subarachnoid migration of the epidural catheter. However, this possibility seems remote in this case in view of the negative aspiration test.

Buprenorphine is highly lipophilic, has a high receptor occupancy and dissociates slowly from the receptor site [2]. Lanz et al. [3] suggested that epidural buprenorphine is absorbed by lipids of the surrounding tissue so well that its concentration is too low to cause respiratory depression during its cephalad spread within cerebrospinal fluid (CSF). In his study, 0.3 mg epidural buprenorphine did not cause any respiratory depression. Therefore, rostral spread of buprenorphine in the CSF after absorption from the epidural space appears to be an unlikely cause of respiratory depression in this case.

Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID), which has been shown to have morphine sparing effects without a central depressant action [4,5]. McQuay [6] has suggested that removing part of the painful input by another analgesic may simply lower the ventilatory depressant dose of the opioid. In this case it seems that this may have occurred when ketorolac was given.

This case report suggests that the dose of epidural opioid when used in combination with an NSAID may need to be adjusted downwards to achieve optimum analgesia with minimal side effects. It highlights the importance of adequate monitoring and the availability of skilled staff in any area in the hospital where patients are receiving epidural opioids.

In conclusion, this case report supports the statement that 'the concept of combination analgesia may be useful but gains in safety from opioid sparing may be partly illusory if pain is itself a counterbalance for opioid induced ventilatory depression' [7].

References