Case report

Respiratory depression following administration of low dose buprenorphine as postoperative analgesic after fentanyl balanced anaesthesia

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Summary

Opioids are among the most ancient and widely used drugs in anaesthesiology. The pharmacology of opioid analgesics and their receptors is a complex and not fully understood matter; even more complex are the interactions between different classes of opioids at both molecular and clinical levels. We want to report here a clinical observation to emphasize the importance of the theoretical basis of anaesthesiology. This paper contains a clinical observation of respiratory depression following the administration of buprenorphine as postoperative analgesic after balanced anaesthesia with fentanyl. The observed case is interpreted in the light of the pharmacokinetics and pharmacodynamics of the different classes of opioid drugs (agonists, agonists–antagonists, antagonists) and of the interactions with their respective receptors.

Keywords: anaesthesia; complications; buprenorphine; fentanyl; pharmacology, respiratory depression

Introduction

The aim of this paper is the critical discussion of a severe and prolonged respiratory depression observed in a young patient following a low dose of buprenorphine administered postoperatively as analgesic after a fentanyl balanced anaesthesia. The pharmacodynamic and pharmacokinetic properties and interactions of the two opioids may be the key to understanding this unusually observed phenomenon.

Case report

An 11-year-old female patient weighing 45 kg was scheduled for surgical correction, by posterior Risser arthrodesis (1), of an idiopathic scoliosis involving 5th to 12th thoracic vertebrae, with a Cobb angle of 46°. Lung function tests and blood gas analysis were carried out preoperatively. The patient was not taking any routine medication and was classified as ASA II. Diazepam 10 mg and atropine 0.5 mg i.m. were administered 90 min before surgery. General anaesthesia was induced with thiopentone 5 mg.kg⁻¹, fentanyl 7 µg.kg⁻¹, dehydrobenzperidol 0.05 mg.kg⁻¹, pancuronium bromide 0.08 mg.kg⁻¹. After tracheal
intubation, mechanical ventilation was started and adjusted to a minute volume of 71 min\(^{-1}\) (\(\text{N}_2\text{O}/\text{O}_2 = 65/35\%\)) to obtain a low grade hyperventilation (Endtidal \(\text{CO}_2\) about 4.5 kPa (35 mmHg)). Fentanyl and pancuronium were administered thereafter according to clinical signs of depth of anaesthesia. Duration of the surgery was 195 min and the procedure was uneventful. The total dose of fentanyl administered during surgery was 19 \(\mu\text{g} \cdot \text{kg}^{-1}\), no halogenated anaesthetic was used. 325 ml of packed red cells were obtained with Haemonetics Cell Saver System and reinfused at the end of surgery along with three units of autologous fresh frozen plasma. After reversal of curarization with neostigmine 0.07 \(\text{mg} \cdot \text{kg}^{-1}\) and atropine 0.02 \(\text{mg} \cdot \text{kg}^{-1}\) the trachea was extubated 25 min after the end of surgery. The patient maintained a stable respiratory pattern with normal \(\text{SpO}_2\) values and three h later was discharged from the recovery room.

All the postoperative laboratory values obtained at six h after surgery were within the normal range. The patient remained calm and pain free until the following morning. No drug was administered during the night, apart from ketoprofen 200 mg as continous infusion (17 \(\text{mg} \cdot \text{h}^{-1}\)) for postoperative analgesia (2). On the first postoperative day, at 07.00, about 12 h after the end of surgery, buprenorphine HCl 4 \(\mu\text{g} \cdot \text{kg}^{-1}\) was administered i.m. after she complained of severe pain and was restless. Three h later a staff anaesthesiologist was requested to treat a respiratory emergency at the patient’s bed. On his arrival, the patient was unconscious, pale and cyanotic with a slow and irregular respiratory rate; carotid pulse was present, full and slow; pupils were miotic, equal and reactive to light. After \(\text{O}_2\) ventilation via Ambu bag and facial mask and verbal/noxious stimulation, rapid recovery of consciousness was obtained without neurological sequelae, apart from retrograde and anterograde amnesia. Arterial gas analysis obtained after mask ventilation demonstrated slight hypercapnia (\(\text{PacO}_2=6.4 \text{kPa (49 mmHg)}\)), and a low haemoglobin, (\(\text{Hb}=8.8 \text{g} \cdot \text{dl}^{-1}\)). She was therefore transferred to the recovery room, where she remained for about two h. During this period, she displayed behaviour typical of opioid overdose i.e., drowsy if not stimulated, bradypnoeic until apnoeic. For these reasons she was admitted to ICU to monitor vital functions. After admission to ICU (13.45 p.m.), the patient became dyspnoeic and agitated. The resident anaesthesiologist in the ICU prescribed 10 mg diazepam i.v. and full respiratory insufficiency appeared again (\(\text{PacO}_2=11 \text{kPa (84 mmHg)}\)). She was intubated and mechanically ventilated with immediate resolution of hypercapnia. To rule out thromboembolism and/or abdominal pathological process, an angiopneumography and ultrasound examination of the abdomen were performed, and both were negative. A marked gastric emptying delay was shown by 950 ml of fluid collected from the nasogastric tube. Gastrointestinal motility resolved spontaneously in two days. The ensuing course was uneventful and the patient was extubated the following morning without any problem and/or sequelae. Three predonated units of autologous packed red cells were administered during the two following days to correct the anaemia typical on 3rd–5th postoperative day after these orthopaedic procedures. Laboratory values relating to this case are reported in Table 1.

**Discussion**

This unusual event of respiratory depression probably represents a classic example of anaesthetic drug interaction. Opioids are a cornerstone of the practice of anaesthesia and are used clinically every day by thousands of physicians. Pharmacology of opioid analgesics and opioid receptors is a very complex and ever changing matter (3–5). Nevertheless, some pharmacodynamic and pharmacokinetic aspects of this class of drugs need to be known by anaesthesiologists and other involved physicians. Fentanyl (6–12) is a lipid soluble opioid with strong agonistic activity, i.e., its intrinsic activity is high because the binding with specific receptors (mu1, mu2, kappa, delta) produces a maximal agonistic effect; clinically it produces all the typical opioid effects in a dose related manner. Fentanyl associates and dissociates rapidly with specific receptors, and its agonistic action is a function of plasma concentration. It was demonstrated that after i.v. administration fentanyl, a basic drug, is stored in the stomach wall and excreted in the gastric juice, and subsequently reabsorbed from the alkaline ambient of the small intestine (8,11). On the other hand, storage of fentanyl in muscle tissue is another particular feature responsible for secondary peaks.
Table 1
Recorded laboratory values

<table>
<thead>
<tr>
<th>Values</th>
<th>After av ICU, before ti ICU, after ti ICU, before te ICU, after te ICU,</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.31 7.01 7.48 7.43 7.42</td>
<td></td>
</tr>
<tr>
<td>$P_{aCO_2}$</td>
<td>(49.5) (64) (34.1) (33.9) (37)</td>
<td>kPa</td>
</tr>
<tr>
<td>$P_{aO_2}$</td>
<td>35 30 24 25 14.5</td>
<td>(mmHg)</td>
</tr>
<tr>
<td>$HCO_3^-$</td>
<td>24.6 21.8 26.3 23.2 25</td>
<td>mmol·l$^{-1}$</td>
</tr>
<tr>
<td>$ABE_c$</td>
<td>-1.1 -9.5 +2.7 +0.1 +1.6</td>
<td>mmol·l$^{-1}$</td>
</tr>
<tr>
<td>$SpO_2$</td>
<td>98.7 99 99.7 98.3 98</td>
<td>%</td>
</tr>
<tr>
<td>$FIO_2$</td>
<td>1 * 0.4 0.3 *</td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>8.8 8.6 8.6 8.0 7.8</td>
<td>g·dl$^{-1}$</td>
</tr>
<tr>
<td>SoC</td>
<td>se un se nr no</td>
<td></td>
</tr>
</tbody>
</table>

SoC = state of consciousness, no = normal, un = unconscious, se = sedated, nr = normal reactivity, av = assisted ventilation, ti = tracheal intubation, te = trachea extubation, ICU = intensive care unit, * = unknown.

in plasma concentrations after resolution of muscle relaxation and during postoperative restlessness (9,13,14). These peculiar pharmacokinetic properties of fentanyl may explain the biphasic respiratory depression reported with the use of fentanyl in nitrous oxide anaesthesia.

Buprenorphine (3,4,12,15) is an opioid derivative of the bainine and its characteristics are complex and still not fully understood. This opioid analgesic was classified as agonist-antagonist, i.e. mu receptor antagonist and kappa receptor agonist. More recently, buprenorphine is classified as partial agonist at both mu and kappa receptors with a peculiar pharmacological and clinical profile characterized by the following features: high lipo- and receptor affinity; slow association with and dissociation from opioid binding sites (slow and prolonged effects); low intrinsic activity (incapable of producing maximal agonistic effects); a characteristic ‘bell’ shaped dose response curve (paradoxical reduction of agonistic effects at greater doses); naloxone may be ineffective as antagonist and/or paradoxically increase the agonistic effects (shift to right of the ‘bell’ shaped dose response curve); doxapram counteracts respiratory depression produced by buprenorphine, probably through activation of carotid chemoreceptors and finally respiratory centres. When fentanyl and buprenorphine are administered in association, the extent and quality of receptor occupancy depend upon the dose of each drug and the timing, so that many different clinical effects and situations are possible. Buprenorphine utilization for intra and/or postoperative analgesia is an established and accepted practice by many anaesthesiologists all over the world and respiratory depression is a linked risk (16–23).

The physiological response to CO$_2$ is influenced by many factors: body temperature, acid-base status, sympathetic and parasympathetic tone, oxygenation, pain perception, drugs, state of consciousness and external stimulation. In the present case, the scoliosis was not so severe and lung function tests and blood gas analysis carried out preoperatively were normal. Surgery was performed to prevent the progression of scoliosis with decline in respiratory function. Nevertheless, it is known that pulmonary function acutely deteriorates postoperatively: the vital capacity decreases and the alveolar–arterial oxygen gradient increases. These alterations of pulmonary functions may require 7–10 days to resolve. In Italy buprenorphine is available as 1 ml vial containing 0.324 mg of buprenorphine HCl (Temgesic, Boeringer Mannheim Italia SpA). The dose actually administered by the nurse was 160 µg of buprenorphine HCl, i.e. half ml of a 1 ml vial from a 1 ml syringe. In the light of the pharmacological properties of opioids used in the present case, we can make the following hypothesis: at the time of buprenorphine administration (small dose, 4 µg·kg$^{-1}$) a concomitant low plasma fentanyl concentration could have been possible, caused by a delayed emptying of the stomach, and mobilization from muscle storage by restlessness. In this way a particular clinical situation was made possible: low plasma fentanyl concentration (full agonist) associated with low plasma buprenorphine

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concentration (partial agonist) resulted in high mu receptor occupancy by both full and partial agonist in a patient with respiratory function compromised by surgery, with resulting respiratory depression. When, in ICU, diazepam 10 mg i.v. was added, this respiratory depression became complete (24–26). The total absence of organic changes demonstrated by all the laboratory and diagnostic evaluations performed and the prompt and complete recovery of the patient on the following day fits in well with this hypothesis. Both the anaesthesiologists involved in this case focused their attention on possible organic postoperative problems (thromboembolism, blood losses, etc.). For this reason angiopneumography and abdominal ultrasound examination were subsequently performed. They were convinced that the administered dose of buprenorphine was too low to explain the clinical situation observed and accordingly doxapram was not administered. In conclusion, this case demonstrates how crucial is the theoretical basis of anaesthesiology. In this particular situation, a more precise knowledge of the pharmacological properties of analgesic drugs could have explained the side effect observed in this patient. Moreover, an objective consideration of the clinical signs could have provided a correct diagnosis and avoided expensive and invasive examinations.

Finally, an accurate evaluation of the case should have suggested that the administration of sedative drugs is contraindicated unless hypoxia and hypercapnia are excluded.

References


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