Use of remifentanil in a patient with chronic hepatic failure

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Summary

We describe a 73-yr-old woman anaesthetized for a laminectomy. She suffered from hepatic failure with mild encephalopathy complicated by several exacerbations associated with sedative and opioid therapy. The challenge for anaesthesia management was to provide adequate analgesia and avoid causing hepatic encephalopathy during and after the surgery. We used remifentanil to provide intraoperative and postoperative analgesia because it has a short duration of action and does not require hepatic metabolism. We closely monitored the respiratory and the neurological status throughout the administration and conclude that remifentanil can provide perioperative analgesia in patients at risk of developing hepatic encephalopathy. (Br. J. Anaesth. 1998; 81: 265–267)

Keywords: liver, cirrhosis; anaesthetics volatile, isoflurane; analgesics opioid, remifentanil; anaesthetics i.v., propofol; complications, hepatic encephalopathy; pain, postoperative; surgery, laminectomy

Remifentanil is licensed in Switzerland for use as an analgesic in the immediate postoperative period, with the supervision of staff trained in the recognition and treatment of the respiratory effects of powerful opioids.

Case report

A 73-yr-old woman suffered from a painful arachnoid cyst at the thoracic level, with a Brown–Séquard syndrome. She was being treated with tramadol (Tramal, Grünenthal), morphine (MST Continus, Mundipharma) and ibuprofen (Brufen, Knoll) medication. She had a 10-yr history of hepatitis C complicated by cirrhosis with frequent minor episodes of memory loss, mild confusion and irritability. She had experienced three episodes of severe hepatic encephalopathy in the preceding eight months, associated with administration of sedative or opioid drugs. The first one was precipitated by a minor gastric ulcer haemorrhage and diazepam (Valium, Roche) medication. The two other episodes occurred without gastrointestinal haemorrhage, but in association with morphine or tramadol administration. Each episode resolved satisfactorily with lactulose, a low protein diet and removal of the likely precipitating drugs. The clinical features of these episodes and EEG findings were characteristic of hepatic encephalopathy rather than simple opioid intoxication.

In order to alleviate her continuous pain, and reduce the drug treatment, surgical resection of the cyst was planned. She had portal venous hypertension, oesophageal varices, and hypersplenism. She had abnormal coagulation factors: prothrombin time: 34 s (normal range: 25–32 s) with factor V at 80% and hypoalbuminaemia (30.8 g litre\(^{-1}\)); a platelet count of 74 000 per 1, Plasma electrolytes and bilirubin were normal. Her general clinical state was good, with no evidence of ascites. Her weight was 75 kg, arterial pressure was 130/70 mm Hg and heart rate 80 beat min\(^{-1}\).

The patient did not receive premedication. Anaesthesia was induced with propofol 2 mg kg\(^{-1}\) (Disoprivan, Zeneca), remifentanil 1 \(\mu\)g kg\(^{-1}\) (Ultiva, Glaxo Welcome) and intubation was facilitated by atracurium 0.5 mg kg\(^{-1}\) (Tracrium, Glaxo Welcome). Anaesthesia was maintained with 50% nitrous oxide/oxygen, isoflurane 0.5–0.8 MAC (Forene, Abbott) and remifentanil infusion at a rate of 0.25 to 0.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\). The monitoring included ECG, arterial pressure by the radial artery catheter, pulse oximetry, rectal temperature, and anaesthetic gas and carbon dioxide analysis. One hour before operation the patient received platelet concentrates and fresh frozen plasma to correct the blood coagulation defect. Intraoperatively 2 litres of crystalloid (glucose 5%-NaCl 0.45%) were administered. After induction of anaesthesia, a decrease in arterial pressure to 85/40 mm Hg necessitated administration of i.v. ephedrine 10 mg to restore the arterial pressure to the preinduction value. Otherwise haemodynamic parameters, blood–gas analysis, blood glucose and electrolyte plasma concentrations remained in the normal range throughout the operation. The duration of the laminectomy was 90 min and the blood loss was minimal.

The remifentanil infusion, isoflurane and nitrous oxide were stopped after skin closure and the lungs ventilated with 100% oxygen. Spontaneous respiration returned 4 min later and the trachea was extubated after 7 min. Immediately after awakening, the pain intensity verbal rating score (VRS; 0 = no pain, 10 = maximum pain imaginable) was zero. Seven minutes later, upon the arrival at the recovery room, the VRS was 7 and a continuous infusion of remifentanil was started at 0.15 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) and the VRS returned to 2 within 7 min. We recorded the VRS

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every 15 minutes during the first 2 h and each hour thereafter. Respiratory rate was monitored throughout the remifentanil infusion. We assessed the neurological status and the presence or absence of flapping tremor every 2 h during the first 48 h and two times a day thereafter. The remifentanil infusion was continued for 48 h in the recovery room at a rate of 0.040 to 0.075 µg/kg/min depending on the patient’s complaints and the VRS. In view of the absence of neurological impairment, ventilatory depression, and the good quality of analgesia, we continued the remifentanil infusion in the ward for 5 days with pulse oximetry and respiratory rate monitoring. Other treatment consisted of a low protein diet (<40 g a day) and oral lactulose. Surgical progress was normal and the patient was discharged after 8 days.

Discussion

Hepatic encephalopathy is not a typical complication of general anaesthesia, but may be related to the use of opioids after operation in patients with severe liver dysfunction. The challenge in our patient was to ensure adequate intraoperative analgesia and postoperative pain relief, without affecting liver function or causing encephalopathy. Regional anaesthesia with local anaesthetics could have been useful but was contraindicated in our patient who had a coagulation defect. Therefore we decided to perform general anaesthesia based on nitrous oxide/oxygen, remifentanil and supplemented by isoflurane and atracurium.

Remifentanil is a mu receptor agonist with analgesic potency similar to fentanyl. It is metabolized by non-specific circulatory and tissue esterases and has a rapid elimination rate. Remifentanil has been studied in patients with severely compromised hepatic function. In these patients the metabolism of remifentanil was not altered and hepatic encephalopathy did not occur. We therefore decided to use remifentanil not only during the operation but also for the postoperative analgesia.

The induction of anaesthesia with propofol and remifentanil provoked a 40% fall in arterial pressure which was rapidly corrected. Otherwise haemodynamic stability was preserved during the operation. Perhaps a smaller dose and slower administration of both drugs might have reduced the hypotension observed on induction of anaesthesia.

Non-steroidal anti-inflammatory drugs are contraindicated for pain relief after operation in patients with liver disease. Two recent studies compared remifentanil and morphine for early postoperative analgesia and showed that remifentanil gave adequate analgesia but with a higher rate of ventilatory depression. Morphine has been largely studied in patients with liver disease and it appears that despite its unchanged metabolism in these patients, there is an increased end-organ sensitivity to this drug. The choice of remifentanil instead of morphine as a postoperative analgesic was based on its rapid elimination if early signs of encephalopathy appeared, on its complete extrahepatic metabolism and on the absence of induced hepatic encephalopathy reported in a recent study. The postoperative infusion rate varied between 0.040–0.075 µg/kg/min, which was the recommended range for healthy patients and slightly higher than for patients with liver disease. We monitored the patient for the appearance of asterixis. Flapping tremor is a good and reliable indicator of hepatic encephalopathy. We did not perform psychomotor tests to detect encephalopathy as they are very difficult to use in the postoperative period. Neither flapping tremor or other signs of neurological impairment appeared after operation in this patient, who had previously developed encephalopathy following opioid administration.

Several pharmacological and pathophysiological factors may contribute to the development of hepatic encephalopathy, which include increased plasma ammonia, aromatic amine and mercaptan levels, altered GABA sensibility, and administration of benzodiazepines and opioids. The effects of opioids are not clear, but like other sedative drugs, they may worsen a pre-existing neurological impairment. Moreover, opioids decrease the propulsive activity of the intestinal tract, so that faecal material remains in the large intestine for a longer time, causing an increased production and resorption of ammonia. Increased ammonia can cause encephalopathy in patients with cirrhosis. There is little information concerning the effect of remifentanil on the gastrointestinal tract but it is probable that this mu agonist has a morphine-like effect. Remifentanil was administered continuously during six days and under these conditions the risk of encephalopathy could not be excluded. However, despite its prolonged administration, we did not observe any neurological symptoms characteristic of hepatic encephalopathy.

Remifentanil is 70% protein bound, probably by alpha-1-acid glycoprotein. We may reasonably assume in this patient with liver disease and reduced plasma proteins, that alpha-1-acid glycoprotein was reduced. Thus the possibility of an overdose caused by an increased free fraction of remifentanil was considered and we carefully titrated the drug to prevent respiratory and neurological complications. Most of the time the administered dose was kept in the range of the usual recommended dose, both during and after the operation.

The other drugs used during anaesthesia are known to have minimal effects on liver function. Isoflurane is known to preserve the total hepatic blood flow and hepatic oxygen supply better than other inhalation anaesthetics at one MAC. Its metabolism is small, minimizing the risk of severe hepatic injury.

A single induction dose of propofol did not prolong the recovery time in cirrhosis.

Atracurium is not dependent on liver function for its elimination. However, the main metabolite, laudanosine, may accumulate in the presence of hepatic impairment and can produce central nervous system excitation. This has never been described to our knowledge following atracurium for intubation.

This case illustrates the successful and safe use of remifentanil for analgesia in a patient with chronic hepatic impairment at high risk of acute hepatic encephalopathy. However, this drug is a powerful analgesic agent which should be used cautiously with adequate respiratory monitoring in a high depen-
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dency ward, especially in patients with hepatic impairment who may have a greater sensitivity to the side effects of the drug.

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References