Optimal dose and timing for perioperative morphine after remifentanil-based anaesthesia

The dose and timing of perioperative morphine following remifentanil-based anaesthesia varies widely in clinical practice.

Remifentanil is a short-acting, selective, μ-opioid receptor agonist that was first approved for use during anaesthesia in 1996. It is rapidly and completely metabolized by blood and tissue non-specific esterases. Its main metabolite, remifentanil acid, has 1 in 300–4600 the activity of remifentanil and is renally excreted. As a potent μ-receptor agonist, remifentanil produces the expected analgesia and sedation along with the expected adverse effects of respiratory depression, nausea, vomiting, muscular rigidity, bradycardia and pruritus.

Remifentanil's unique pharmacokinetic profile delivers a predictable onset and offset of effect. It has a context-sensitive half life (the time necessary to achieve a 50% decrease in blood concentration after termination of a variable length, continuous infusion targeted to maintain a steady state concentration, where the 'context' is the duration of the infusion) of 3–4 minutes (Egan et al, 1993). Its terminal half-life is 10–20 minutes (Westmoreland et al, 1993).

The context-sensitive half-life of remifentanil has allowed high-dose infusions to be run intraoperatively for stimulating procedures while avoiding the unwanted postoperative side effects of high-dose opioids. However, this pharmacokinetic profile of remifentanil also means that the profound analgesic effect is terminated within 3–4 minutes of cessation of the infusion. In order to provide adequate postoperative analgesia it is sometimes necessary to supplement the remifentanil-based anaesthetic technique with perioperative morphine. The timing of this morphine dose varies considerably in current anaesthetic practice.

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Timing of perioperative morphine

Morphine's peak analgesic effects are reported as being between 10 (Peck et al, 2003) and 40 minutes after administration (Sarton et al, 2000). Waiting 20 minutes after intravenous administration of morphine before carrying out a painful procedure is widely accepted. Akrofi et al (2005) showed that intravenous morphine given 20 minutes before the removal of chest drains significantly reduces procedural pain. When using remifentanil-based anaesthesia, morphine is commonly given 20–30 minutes before the end of surgery (Yarmush et al, 1997; Fletcher et al, 2000), although this is not in keeping with the reported time to maximal analgesic activity of morphine, which is as long as 40 minutes in human volunteers (Sarton et al, 2000).

This is given clinical relevance by an adequately powered, prospective, randomized blinded placebo-controlled study by Munoz et al (2002). This showed that better early postoperative pain control is achieved when intraoperative morphine is given more than 40 minutes before the end of surgery. The study randomly assigned 120 adult patients undergoing laparoscopic cholecystectomy to one of four groups. Group 1 received a placebo. Group 2, 3 and 4 received 0.15 mg/kg morphine at <20 minutes (group 2), 20–40 minutes (group 3) and >40 minutes (group 4) before the end of surgery. The group that received the morphine more than 40 minutes before the end of surgery was the only one showing reduced morphine consumption in the post anaesthetic care unit compared to placebo. Remifentanil when used with other short-acting agents facilitates an early recovery from anaesthesia. Munoz et al (2002) also showed that the timing of intraoperative morphine has no significant effect on early recovery from anaesthesia.

Dose of perioperative morphine

Another consideration when using remifentanil-based anaesthesia is its antanalgesic effect and the increase in postoperative morphine requirements. Should a larger dose of morphine be given intraoperatively? A prospective, randomized study (Fletcher et al, 2000) of 245 patients who underwent remifentanil-based anaesthesia compared perioperative morphine doses of 0.25 mg/kg and 0.15 mg/kg given 30 minutes before the end of surgery. Although the larger dose slightly improved postoperative analgesia, it did not prevent additional morphine requirements in the post anaesthetic care unit and was associated with an increased incidence of respiratory depression.

Conclusions

From the published evidence and pharmacokinetic data, a perioperative morphine dose of 0.15 mg/kg, given 40 minutes before the end of surgery, is the optimal regimen for reducing postoperative pain following remifentanil-based anaesthesia. BJHM

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