

Remifentanil to treat hypertension in overweight patients during a fentanyl-based cardiac anesthesia A case series

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ABSTRACT

Cardiac surgery is associated with intense nociceptive and autonomic stimulation especially during sternotomy and aortic root dissection and moderate-to-high dose opioids are required to blunt the hemodynamic and neuroendocrine response to this kind of procedures. However, episodes of unwanted sympathetic activation leading to intraoperative hypertension are not always preventable with a fentanyl-based anesthesia regimen and antihypertensive drugs without anesthetic properties are added to obtain hemodynamic stability. We report on five cardiac surgical cases in which intraoperative hypertension unresponsive to incremental doses of fentanyl was successfully treated adding a remifentanil target-controlled infusion instead of a non-anesthetic vasoactive drug. This approach could help to avoid the dilemma: when should we stop adding anesthetics and switch to antihypertensive drugs in cardiac surgery?

Keywords: *Remifentanil, Fentanyl, Anesthesia, Cardiac anesthesia, Hypertension.*

INTRODUCTION

Fentanyl is still very commonly used in anesthesia for cardiac surgery. A time-honored drug in this setting, with low cost among its many advantages, it has been used in a wide range of dosages in all kind of cardiac surgical procedures. Since it is characterized by an important context-sensitive half-life mainly due to its high liposolubility (1), it is an unsuitable drug for precise intraoperative analgesia titration.

Remifentanil is widely accepted as a safe and effective drug in cardiac anesthesia. Its very short onset time, ultra rapid metabolism and the lack of context-sensitive half-

life make it an appealing drug for both tight intraoperative analgesic control and for rapid postoperative recovery (2).

Fentanyl and remifentanil, both in combination with an hypnotic agent, are today considered alternative choices in cardiac anesthesia (3, 4). Their concomitant use within the same surgical procedure was rarely described and only in the setting of research protocols (5, 6).

We hereby describe five cardiac surgical cases in which a remifentanil target-controlled infusion (TCI) was added to a high-dose-fentanyl/sevoflurane anesthesia regimen to control intraoperative hypertension.

CASE REPORT

All five cases were operated at our center between January and June 2007. After

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Table 1 - Characteristics of five cardiac surgical cases in which a remifentanyl target-controlled infusion (TCI) was added to a high-dose-fentanyl/sevoflurane anesthesia regimen to control intraoperative hypertension.

Patient	Age	Sex	Procedure	Weight	Height	BMI	LVEF	Preoperative medications
1	74	F	CABG	78	162	29.8	51 %	ASA, β -blocker, ACE-I, PPI, Insulin
2	68	F	CABG + Mitral valve repair	67	159	26.6	42 %	ASA, β -blocker, ACE-I, Nitrates
3	76	M	CABG + Aortic valve replacement	97	178	30.7	61 %	ASA, ACE-I, Statin, Coumadin, Nitrates
4	68	M	CABG	88	180	27.2	60 %	ASA, β -blocker, ACE-I, Statin, Nitrates, Heparin
5	60	M	CABG	107	175	35.0	54 %	ASA, β -blocker, ACE-I, PPI, Nitrates, Heparin

Legend:

F: female; M: male; CABG: coronary artery bypass graft; BMI: body mass index; LVEF: left ventricle ejection fraction; ASA: acetylsalicylic acid; ACE-I: angiotensin converting enzyme inhibitor; PPI: proton pump inhibitor; Weight in kg; Height in cm.

ethical committee approval and patients' written consent we collected patients characteristics and procedures as summarized in Table 1. Notably all patients were overweight. In all patients angiotensin-converting enzyme inhibitors were stopped 24 hours before surgery. All the patients were premedicated with subcutaneous morphine and oral diazepam. Anesthesia was induced with fentanyl 2-4 $\mu\text{g}/\text{kg}$, thiopental 3-5 mg/kg and succinylcholine 1 mg/kg and maintained with sevoflurane 1-2% end-tidal, fentanyl and vecuronium. All the patients were normotensive or hypotensive between induction and skin incision. Before skin incision fentanyl dose was incremented at at least 12 $\mu\text{g}/\text{kg}$ and subsequent boluses were titrated to hemodynamic response. In all the described patients hypertension (systolic arterial pressure > 140 mmHg) developed during mediastinal dissection or conduits harvesting and total fentanyl dose was brought up to 45-51 $\mu\text{g}/\text{kg}$, without satisfactory effects in terms of control of the hemodynamic response. Remifentanyl TCI was started at a target concentration of 3-8 ng/ml (effect-site). In all five patients rapid control of hypertension was achieved with-

in few minutes without the need to use an antihypertensive drug. While on cardiopulmonary bypass remifentanyl infusion was titrated to obtain an arterial pressure between 60 and 80 mmHg with a pump flow of at least 2,4 l/min/m². This goal was achieved in all patients with an effect-site concentration between 3 and 15 ng/ml. Remifentanyl infusion was maintained throughout the interventions and gradually tapered before leaving the operating room, when a propofol infusion was started. All patients were discharged from the hospital within two weeks from the intervention.

DISCUSSION

During cardiac surgical procedures intense nociceptive and autonomic stimulation is evoked by sternotomy, mediastinal dissection and aortic root manipulation. Even if synthetic opioids, the mainstay of modern cardiac anesthesia, are able to control the hemodynamic and neuroendocrine reaction to these profoundly antiphysiologic situations, their clinical efficacy can be partly influenced by patient-specific char-

acteristics that are often difficult to anticipate and impossible to modulate like interactions with preoperative medications, body-compartments drug distribution and individual sensitivity. As a consequence, unwanted episodes of breakthrough or persistent sympathetic activation could happen in some patients during cardiac surgical procedures even when the depth of anesthesia and analgesia were considered sufficient to prevent them and vasoactive drugs (β -blockers or vasodilators) are often used in these situations (7).

We think that this could be in some cases the result of the difficulty in modulating μ opioid receptor agonism with a drug, like fentanyl, with a pharmacokinetic profile unsuitable to rapidly and precisely adapt the analgesic effect to the magnitude of the surgical stimulation in the different phases of the operation.

In the cases described in our report we overlapped a remifentanyl TCI on our standard fentanyl-based anesthesia protocol after we hypothesized that the signs of uncontrolled sympathetic activation were caused by the incapacity to reach an adequate μ opioid receptor stimulation with what we considered an already adequately high fentanyl dose.

We thought therefore that using only a vasodilator without antinociceptive activity, like sodium nitroprusside, nitroglycerine or urapidil, would not had been the best choice in this situation because it wouldn't had had any effect on the depth of analgesia and on the stress-response control while it is well demonstrated that opioids are able to effectively blunt the neuroendocrine response to surgery. In all the described cases this approach proved effective in rapidly regain control of the patient's hemodynamic. We cannot, however, completely exclude that the noted hemodynamic effect of remifentanyl was mediated through a different mechanism than μ opioid receptor

stimulation, like direct vasodilatation, as was demonstrated to happen in an animal study (8). In a clinical study on patients with total artificial hearts under fixed cardiac output conditions, remifentanyl was shown to induce dose-dependent, rapidly-reversible systemic arterial vasodilatation without any effect on pulmonary vascular resistance and on left and right atrial pressure (9). Remifentanyl appears therefore to be a particularly interesting drug for the treatment of hypertension in the cardiac anesthesia setting.

All the described patients were either overweight (BMI > 25) or obese (BMI > 30, see *Table 1*). Fentanyl is known to be highly lipid-soluble and its continuous redistribution in adipose tissue could have led to insufficient plasma and effect-site concentration explaining the difficulty in gaining a stable clinical effect even after total administered dose approached or reached 50 $\mu\text{g}/\text{kg}$ and despite the concomitant administration of sevoflurane. Remifentanyl has a much smaller volume of distribution than fentanyl and this could have led to better preserved effect-site concentration in our patients.

Untoward circulatory effects were described while using remifentanyl in cardiac surgery but in this case series the use of the Minto TCI model proved very effective in gradually titrate the effect of the drug and we did not experience any episodes of uncontrolled hypotension or bradycardia.

In conclusion, in this case series of overweight patients, a remifentanyl TCI was effective in controlling hypertension when adequate hemodynamic control could not be achieved with the ongoing fentanyl-based anesthesia protocol. Whether this approach has real advantages over the use of vasoactive drugs without analgesic properties remains to be proven.

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REFERENCES

1. Stoelting RK. Pharmacology and physiology in anesthetic practice (ed 4). Philadelphia, PA, Lippincott Williams & Wilkins. 2006; 104-105.
2. Lison S, Schill M, Conzen P. Fast-track cardiac anesthesia: efficacy and safety of remifentanil versus sufentanil. *J Cardiothor Vasc Anesth.* 2007; 21: 35-40.
3. Engoren M, Luther G, Fenn-Buderer N. A comparison of fentanyl, sufentanil, and remifentanil for fast-track cardiac anesthesia. *Anesth Analg.* 2001; 93: 859-864.
4. Myles PS, Hunt JO, Fletcher H, et al. Remifentanil, fentanyl, and cardiac surgery: a double-blinded, randomized, controlled trial of costs and outcome. *Anesth Analg.* 2002; 95: 805-812.
5. Pleym H, Stenseth R, Wiseth R, et al. Supplemental remifentanil during coronary artery bypass grafting is followed by a transient postoperative cardiac depression. *Acta Anesthesiol Scand.* 2004; 48: 1155-1162.
6. Rauf K, Vohra A, Fernandez-Jimenez P, et al. Remifentail infusion in association with fentanyl-propofol anaesthesia in patients undergoing cardiac surgery: effects on morphine requirement and postoperative analgesia. *Br J Anaesth.* 2005; 95: 611-615.
7. Sprigge JS, Wynands JE, Whalley DG, et al. Fentanyl infusion anesthesia for aortocoronary bypass surgery: plasma levels and hemodynamic response. *Anesth Analg.* 1982; 61: 972-978.
8. Unlugenc H, Itegin M, Ocal I, et al. Remifentanil produces vasorelaxation in isolated rat thoracic aorta strips. *Acta Anesthesiol Scand.* 2003; 47: 65-69.
9. Ouattara A, Boccara G, Koehler U, et al. Remifentanil induces systemic arterial vasodilation in humans with a total artificial heart. *Anesthesiology.* 2004; 100: 602-607.