Anesthesiology
1997; 87:1019-20

Severe Bradycardia after Remifentanil

To the Editor:—In the past few months, our institutional practice for cardiovascular anesthesia at the VA Medical Center, Miami, Florida, has changed to include remifentanil (Ultiva, Glaxo Wellcome, Research Triangle Park, NC), an ultra-short-acting opioid agonist with a rapid onset and offset of action. This property makes this drug very attractive for use in cardiothoracic procedures when the aim is early postoperative extubation (so-called "fast-tracking"). However, we have now encountered six cases of severe bradycardia (heart rate < 30 beats/min) and hypotension (systolic blood pressure < 80 mmHg) after a bolus dose of remifentanil 1 μg/kg, followed by a continuous infusion of 0.1-0.2 μg/kg, delivered *via* a Medfusion 2010i (Medfusion Inc., Duluth, GA) syringe infusion pump, in patients undergoing coronary artery bypass graft (CABG) surgery. These six cases occurred as part of the first 30 patients anesthetized with this drug. All patients responded immediately to intravenous administration of ephedrine and to temporary discontinuation of the remifentanil infusion. We report here the sequence of events for one these six cases.

A 54-yr-old man (height, 177 cm; weight, 91 kg) was scheduled to undergo a four vessel CABG. His medical history was significant for two myocardial infarctions in 1990 and 1994, stable angina, hypertension, and anxiety disorder. Medications included metoprolol 50 mg twice daily, isosorbide dinitrate, sublingual nitroglycerin, and temazepam. Cardiac catheterization revealed critical stenoses of the left anterior descending, circumflex, and right coronary arteries. His ejection fraction was reported to be 50%. The patient was given his usual dose of metoprolol 2 h before surgery, and preoperative medications (morphine, 5 mg; midazolam, 2 mg; scopolamine, 0.4 mg; intramuscularly) approximately 1 h before surgery. After placement of noninvasive monitors (blood pressure cuff, electrocardiograph, SpO_2), intravenous midazolam 2 mg was administered, and an arterial catheter was inserted in the left radial artery. Induction of general anesthesia was achieved as follows: the patient was asked to breathe 100% oxygen *via* a mask for 3 min, and 1 mg of intravenous pancuronium was given. Remifentanil, 1 μg/kg bolus, was administered *via* a 2010i syringe pump, followed by an infusion of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 10 mg of intravenous etomidate (Amidate, Abbott Labs). The patient's lungs were easily ventilated with 100% oxygen, and pancuronium 9 mg was given. Approximately 2-3 min after the remifentanil bolus, it was noted that the heart rate (HR) had decreased to 30 beats/min, and the systolic blood pressure (SBP) was 70 mmHg. Direct laryngoscopy and tracheal intubation were performed immediately, with the expectation that this would increase HR and SBP. When this response did not occur, the remifentanil infusion was stopped, and intravenous ephedrine 10 mg was administered. This dose was repeated in about 3 min because the initial response was slow. HR increased to 80 beats/min, and SBP to 130 mmHg. The remifentanil infusion was restarted and adjusted between 0.1-0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, supplemented by sevoflurane to control blood pressure and ensure unawareness. The rest of the case, including the postoperative course, was uneventful, and the patient was discharged home on postoperative day 5.

Remifentanil is a very short-acting opioid agonist, recently approved for use in the United States. The package insert recommends that bolus doses of remifentanil be given over 30-60 s to minimize the incidence of muscular rigidity. However, bradycardia is not mentioned. Among the first 30 patients anesthetized with remifentanil, bolus doses were given to eight, and bradycardia (< 30 beats/min) and hypotension (< 80 mmHg) developed in six of these. The starting HR in the patients who developed bradycardia ranged from 55 to 94 beats/min, and was similar in the patients who did not develop bradycardia. Interestingly, we have never encountered muscular rigidity. This may be due to our clinical practice of pretreatment with a nondepolarizing muscle relaxant. In one of our patients who developed bradycardia, the remifentanil infusion and other agents used for induction of anesthesia were administered in the same intravenous line. This particular patient may have received an inadvertent overdose of remifentanil.

It is generally accepted that the cause of opioid-induced bradycardia is vagally mediated. Bilateral vagotomy has been shown to abolish this effect.[1] Speed of injection is also an important factor, and clinical experience suggests that bradycardia may be minimized by slow administration.[2] The Medfusion 2010i syringe infusion pump delivers a bolus of 1 μg/kg (remifentanil concentration of 50 μg/kg) at the rate of 10 μg every 4 s. Therefore, it takes the pump 24 s to deliver a bolus to a 60-kg patient, 28 s for a 70-kg patient, and so on. This is faster than the recommended rate of 30-60 s for a bolus dose. We have now discontinued using 1 μg/kg boluses, and are instead using smaller boluses of 0.3-0.5 μg/kg.

There is a higher incidence of bradycardia in anesthetized than in awake subjects,[1] and also a higher incidence when breathing 100% oxygen than nitrous oxide and oxygen.[3] Our patients were ventilated with oxygen, and also received etomidate or propofol as part of the induction technique. The presence of β-adrenergic or calcium-channel blockade is another predisposing factor. Although 3 of 6 patients who had bradycardia were on β-blockers, so were 13 of 24 who did not receive a remifentanil bolus and did not develop bradycardia. None of our patients were on a combination of β- and calcium channel blocking agents. There is a report of an intraoperative adverse event (HR, 30-35/min; SBP < 70 mmHg) in a patient receiving remifentanil who was also on concomitant metoprolol.[4] Administration of muscle relaxants with no vagolytic properties (*e.g.*, vecuronium)[5] or vagotonic properties (succinylcholine)[6] has also been cited as a cause of bradycardia. However, we could detect no correlation between the various muscle relaxants we used to facilitate tracheal intubation and the occurrence of bradycardia (table 1). Two of 6 patients who had bradycardia and 6 of 24 who had no bradycardia also received 1.5-2 mg of intrathecal morphine at the L3-L4 lumbar interspace before induction of anesthesia. Bradycardia has been reported in dogs given 5 mg of intrathecal morphine,[7] and in humans

Table 1. Patients Who Received Remifentanil for Coronary Artery Bypass Graft: Comparison of Drugs Administered to Patients who Developed Bradycardia *versus* Patients who Did Not Develop Bradycardia

Drugs Administered	Patients who Had Bradycardia (n = 6)	Patients who Did Not Have Bradycardia (n = 24)
Induction agent		
Etomidate	4	13
Propofol	2	6
Thiopental	0	5
Muscle relaxant		
Succinylcholine	1	5
Cisatracurium	3	5
Vecuronium	0	1
Pancuronium	2	13
Inhalation agent		
Isoflurane	0	6
Sevoflurane	6	18
Concomitant medications		
Beta-adrenergic blockers	3	13
Calcium channel blockers	1	3
Digoxin	1	1
ACE inhibitors	3	7
Intrathecal morphine	2	6
Remifentanil bolus (1 μg/kg)	6	2

after epidural or intrathecal administration of sufentanil.[8] Our dose of intrathecal morphine was well below the one used in dogs, and we did not administer intrathecal sufentanil. We do not believe that the intrathecal morphine contributed to the bradycardia. The most likely mechanisms for opioid-induced hypotension are a centrally mediated decrease in sympathetic tone and vagally induced bradycardia. Because remifentanil has a rapid onset of action, this seems to be the most likely explanation for the hypotension accompanying the bradycardia.

Gerard DeSouza, M.D.
Assistant Professor of Anesthesiology
Michael C. Lewis, M.D.
Assistant Professor of Anesthesiology
Menno F. TerRiet, M.D.
Research Fellow in Anesthesiology
Veterans Affairs Medical Center
University of Miami School of Medicine
Anesthesiology Service (139)
1201 N.W. 16th Street
Miami, Florida 33125

References

1. Reitan JA, Stengert KB, Wymore MC, Martucci RW: Central vagal control of fentanyl-induced bradycardia during halothane anesthesia. Anesth Analg 1978; 57:31-6

2. Liu WS, Bidwai AV, Stanley TH, Isern-Amaral J: Cardiovascular dynamics after large doses of fentanyl and fentanyl plus N_2O in the dog. Anesth Analg 1976; 55:168-72

3. Prakash O, Verdouw PD, DeJong JW, Meij SH, Van der Borden SG, Dhasmana KM, Saxena PR: Haemodynamic and biochemical variables after induction of anaesthesia with fentanyl and nitrous oxide in patients undergoing coronary artery by-pass surgery. Can Anaesth Soc J 1980; 27:223-9

4. Dershwitz M, Randel GI, Rosow CE, Fragen RJ, Connors PM, Librojo ES, Shaw DL, Peng AW, Jamerson BD: Initial clinical experience with remifentanil, a new opioid metabolized by esterases. Anesth Analg 1995; 81:619-23

5. Starr NJ, Sethna DH, Estefanous FG: Bradycardia and asystole following the rapid administration of sufentanil with vecuronium. ANESTHESIOLOGY 1986; 64:521-3

6. Sherman EP, Lebowitz PW, Street WC: Bradycardia following sufentanil-succinylcholine. ANESTHESIOLOGY 1987; 66:106

7. Sabbe MB, Grafe MR, Mjanger E, Tiseo PJ, Hill HF, Yaksh TL: Spinal delivery of sufentanil, alfentanil, and morphine in dogs. ANESTHESIOLOGY 1994; 81:899-920

8. Houweling PL, Ionescu TL, Hoynck Van Papendrecht AAGM, Schimmel GH, Verkooyen R, Smalhout B: A haemodynamic comparison of epidural versus intrathecal sufentanil to supplement general anaesthesia for abdominal aortic surgery. Eur J Anaesth 1992; 9:95-103

(Accepted for publication July 7, 1997.)