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Acute and life-threatening remifentanil overdose resulting from the misuse of a syringe pump

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Abstract : In the perioperative setting, syringe pumps are frequently used. They guarantee constant plasma levels of hypnotics, opioids, cardiovascular medication, insulin or other drugs. We present a case in which an inadvertent rapid intravenous injection of 2 mg remifentanil occurred due to the misuse of a syringe pump.

Key words : Remifentanil ; syringe pump ; critical incident ; difficult airway.

Introduction

In the perioperative setting, syringe pumps are frequently used. They guarantee constant plasma levels of hypnotics, opioids, cardiovascular medication, insulin or other drugs. We present a case in which an inadvertent rapid intravenous injection of 2 mg remifentanil occurred due to the misuse of a syringe pump.

Case Report

A 71-year-old, male patient (weight : 73 kg, height : 180 cm) was scheduled for the endovascular place-ment of an iliac branch prosthesis in order to correct an arterial aneurysm of the right common iliac artery and the right internal iliac artery. The past medical history included 30 pack-years of tobacco abuse (with smoking cessation in 2000), arterial hypertension (treated with nebivolol, amlodipine, olmesartan), hypercholesterolemia (treated with pravastatine) and an acute myocardial infarction in 2006, for which a drug-eluting stent had been placed in the left anterior descending artery (secondary prevention with low dose acetylsalicylic acid).

For induction of total intravenous anesthesia, standard anesthesia monitors (non-invasive measurements of arterial blood pressure, 5-lead-electrocardiography, pulse-oximetry) were connected to the patient. A 16 G intravenous catheter (BD Insyte-W, Becton Dinckinson Infusion Therapy Systems Inc., Utah, USA) was placed in a dorsal vein of the left hand and connected to a triple lumen infusion device with three non-return valves (Octopus 3, Vycon, Ecouen, France). The first lumen was connected to a balanced crystalloid infusion (PLASMA-LYTE A, Baxter S.A., Lessines, Belgium). The second lumen was connected to a 50 ml prefilled propofol syringe (Diprivan 1%, AstraZeneca, Brussels, Belgium) through a 200-cm long, rigid extension tube (Original Perfusor Line, B. Braun, Melsungen, Germany). The third lumen was connected in the same way to a 50 mL syringe (Original Perfusor Syringe 50 mL, B. Braun, Escholzmatt, Switzerland) filled with remifentanil (Ultiva, GlaxoSmithKline Pharmaceuticals, Wavre, Belgium), 20 mL at a concentration of 100 μg/mL, equaling a total dose of 2 mg. Before connection to the patient, all tubing had been thoroughly flushed with the corresponding medications to evacuate all remaining air. Both syringes were placed horizontally into the syringe pumps (Alaris PK Syringe Pump, CareFusion, Rolle, Switzerland) that were fixed approximately 100 cm above the patient's heart level.

For the continuous monitoring of arterial blood pressure, the right arm of the patient was prepared for catheterization of the radial artery while awake. During puncturing, the right arm of the patient suddenly became spastic. The patient was unresponsive to both verbal and tactile stimulation. At this moment we noted that the remifentanil syringe was completely empty. We

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Informed consent of the patient for publication of this case report was obtained.

also noticed that the plunger of the syringe was not locked in the pusher lever. These observations were suggestive for the diagnosis of an acute overdose of remifentanil due to an inadvertent bolus injection of 20 mL (2 mg) remifentanil. The left arm of the patient became also spastic at that time. Both legs showed a tonic-clonic seizure behavior, while the upper limbs developed flexion contracture, making accurate non-invasive measurement of arterial blood pressure impossible. The carotid pulse could still be palpated. The patient's heart rate decreased from 80 beats min^{-1} to 65 beats min^{-1}. Soon, the patient became apneic, and peripheral saturation decreased. An attempt was made to manually ventilate the patient through a face mask, which was however not successful, because of severe muscle rigidity of the chest. Due to an extreme spasm of both masseter muscles, the mouth of the patient could not be opened, for the placement of an endotracheal tube or a supraglottic device. The minimal measured saturation at that moment was 61 %. Therefore, we made the decision to immediately induce general anesthesia with an intravenous infusion of propofol (target controlled infusion, Marsh model, 4.0 μg mL^{-1}) and rocuronium bromide 50 mg (Esmeron, Organon, Oss, Nederland). Thirty seconds later, the patient's musculature started to relax and manual ventilation became possible. The trachea of the patient was intubated and the patient was mechanically ventilated. Next, the right radial artery was cannulated, revealing an arterial blood pressure of 94/46 mmHg. Total intravenous anesthesia was maintained using propofol (target-controlled infusion, Marsh model, 4.0 μg mL^{-1}) and remifentanil (0.1 μg Kg^{-1} min^{-1}). The surgical procedure was performed as scheduled, and was uneventful. After the end of surgery, the patient awoke 6 minutes after discontinuation of anesthesia. The patient was repeatedly evaluated: immediately after extubation, one hour after surgery in the recovery room, and thirty hours after surgery on the surgical ward. No adverse events could be documented. When answering the Brice questionnaire during the last post-anesthesia visit, the patient did not report any explicit awareness of the event. The last thing he could remember was that, before entering the operating room, one of the nurses placed a surgical cap on his head.

Discussion

The inadvertent administration of high doses of remifentanil have been described as a consequence of defective syringe pumps (1), accidental bolus administration (2) and dose miscalculation (3). In our case, the syringe plunger had accidentally not been locked in the pusher lever of the syringe pump, allowing remifentanil to be evacuated as a bolus into the patient. Similar mishaps with syringe pumps have been described with morphine and midazolam (4), and with a patient-controlled analgesia pump (5).

The physics underlying this accident have been previously described in detail by Shenkman *et al* (4). Briefly, given the fact that the patient's arm was positioned 100 cm lower than the syringe pump, the syringe plunger was displaced by the negative hydrostatic force resulting from this level difference between the intravenous catheter and the syringe (4). Additionally, the evacuation of the syringe might have been facilitated by the Venturi effect, elicited by the high-flow crystalloid infusion that was connected to the multilumen infusion device and hence indirectly also to the remifentanil syringe.

We reproduced this incident using the same setting, however without patient and replacing remifentanil with a saline solution. After unlocking the pusher lever from the plunger, the syringe emptied spontaneously through the rigid extension tube into the fast-running infusion. Within less than 4 minutes, the total syringe volume of 20 mL had emptied. Our patient received 2 mg remifentanil over a time span of only a few minutes. A normal induction dose for this patient would be approximately 0.04 - 0.08 mg in one minute. This means that we inadvertently administered at least a 25-fold normal induction dose. We simulated the time course of the plasma concentration of remifentanil in this patient using a simulation program (RUGLOOP II, DEMED, Temse, Belgium), loaded with the compartmental pharmacokinetic model as published by Minto *et al* (6, 7). We found that this bolus administration resulted in a calculated plasma concentration of remifentanil of approximately 150 ng mL^{-1}, a 30-fold normally targeted plasma concentration (8).

Due to this massive overdose in our case, almost all side effects of remifentanil became instantaneously obvious : sedation, rigidity of skeletal striated muscles, bradycardia (although not so marked in this case), respiratory depression and apnea (8).

In this case, we were alerted by the spasticity and the tonic-clonic seizure of the patient. Normally, one would expect that desaturation would be the first sign of such a high dose of remifentanil. We believe that, due to the fast infusion of the medication and the rapid onset of remifentanil, the plasma

concentration for muscle rigidity and seizure was reached so quickly, that the patient did not had the time to desaturate.

To the best of our knowledge, equally high doses of remifentanil in non-anesthetized and non-intubated patients have only been used and described in preclinical pharmacokinetic studies (9). Also in these studies, muscle rigidity was observed as a major side-effect and had to be treated with a continuous infusion of succinylcholine, to allow mask ventilation.

The literature is silent about the appropriate management of such a remifentanil overdose. It could be argued that antagonizing remifentanil with naloxone might have been a suitable therapeutic approach. For opioid overdoses, the prescribing information of naloxone(10) recommends repetitive doses of 0.4 mg-2 mg until a total dose of 10 mg has been achieved. In our hospital, only ampullas of 0.4 mg of naloxone (Naloxone B. Braun 0.4 mg. mL^{-1}, 1 mL, Melsungen, Germany) are available. Hence, the preparation of up to 10 mg naloxone would have been too time-consuming in order to prevent hypoxemia.

Waiting for spontaneous metabolization of remifentanil would have also taken too long. The spontaneous recovery of ventilation can only be expected at a remifentanil plasma concentration of around 2 ng mL^{-1} (8), and a large interindividual variability exists. The applied pharmacokinetic modeling shows that this concentration would have been reached only 35 minutes after the termination of the accidental infusion.

One could argument that immediately starting an intravenous infusion of propofol is, maybe, not necessary, insofar as a plasma concentration of remifentanil of 150 ng mL^{-1} is enough to guarantee unconsciousness and amnesia. However, propofol was added immediately for two reasons. First, at the moment of the acute event, we did not know what the plasma concentration of remifentanil was. We knew it would be high, but there was no time to calculate the exact plasma concentration. Since there were no signs of hemodynamic instability, propofol was added to guarantee unconsciousness and amnesia. Secondly, since propofol also gives a certain degree of muscle relaxation, it was added to optimize intubation conditions.

In our case, with apnea, the impossibility of mask ventilation and instrumentation of the upper airway, a rapid induction of general anesthesia, muscle relaxation, subsequent endotracheal intubation and mechanical ventilation seemed the only and best available option.

Conclusion

Although frequently neglected by caregivers, the safe use of syringe pumps requires continuous attention and thorough understanding of the underlying physics and possible sources of error.

We present a case in which an accidental overdose of remifentanil occurred because the syringe plunger had accidentally not been locked in the pusher lever, allowing the spontaneous evacuation of the syringe. A comparable incident outside the setting of a fully equipped anesthesia working place would have certainly been associated with major morbidity or even mortality of the affected patient. It is therefore important to note that any drug infusion should be connected to the patient only after the correct assembly of the syringe pump installation has been checked. Users must verify that the syringe plunger is properly secured to the pusher lever. Moreover, intravenous infusion lines containing vasoactive drugs or potent anesthetic drugs ideally need anti-reflux valves. A further preventive measure would be to place syringe pumps only below the patient's heart level. At last the anesthesiologist should only turn the stopcock of the entry of the intravenous medication when he/she is sure that everything has been checked and safe administration of the medication can be guaranteed.

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