CASE REPORT

Atropine sulfate for treatment of bradycardia in a patient with morbid obesity: what may happen when you least expect it

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SUMMARY

A 74-year-old morbidly obese man was scheduled for surgical repair of an incisional ventral hernia. Anaesthesia was induced with propofol and fentanyl, and maintained with desflurane. A second dose of fentanyl 0.2 mg, given before starting surgery, resulted in sinus bradycardia and mild decrease of arterial blood pressure. Atropine sulfate 0.5 mg was administered. One minute later, the ECG rhythm on the monitor changed to third degree atrioventricular block with a ventricular response rate of 40 beats/min associated with marked hypotension. Isoproterenol 0.02 mg reverted the atrioventricular block to sinus rhythm. Cardiac enzymes and ECG ruled out acute myocardial ischaemia. The surgical procedure and the recovery from anaesthesia were uneventful. The patient was discharged from the hospital on the fifth postoperative day. For the treatment of bradycardia atropine sulfate should be adjusted at least to lean body weight in order to avoid paradoxical heart rate response in patients with obesity.

BACKGROUND

The adequate administration of anaesthetic drugs is essential for optimal anaesthesiological management of patients with morbid obesity (MO). Knowledge of their proper dosing scalar represents a crucial aspect for the safe and effective administration of anaesthetic drugs in patients with MO.¹⁻³ Atropine sulfate is a drug commonly used in anaesthesia. Its inadequate administration for the treatment of bradycardia may not be free of complications.⁴⁻⁶ There is a paucity of information on whether and how dosing of atropine sulfate should be adjusted in patients with MO.¹⁻³ It is important to underline the correct dosing regimen for atropine sulfate in patients with MO.

CASE PRESENTATION

A 74-year-old MO man was scheduled for surgical repair of an incisional ventral hernia. His medical history included chronic obstructive pulmonary disease and arterial hypertension for which he was taking ACE inhibitor orally. He had undergone low anterior resection for rectal cancer 1 year earlier. Preoperative routine laboratory testing, ECG and chest radiography were normal.

After overnight fasting, an 18-gauge intravenous line was placed in the arm and an infusion of saline solution established. Before anaesthesia, the patient was premedicated by intravenous administration of midazolam 3 mg and ranitidine 50 mg. Anaesthesia

was slowly induced with propofol 200 mg and fentanyl 0.2 mg. After receiving rocuronium 70 mg, tracheal intubation was easily performed. Lung ventilation was set to positive end-expiratory pressure at 5 cm H₂O and peak inspiratory pressure in order to obtain a tidal volume of 10 mL/kg (ideal body weight), respiratory rate of 12 breaths/min and inspiratory:expiratory ratio of 1:1. Anaesthesia was maintained with desflurane in oxygen/air mixture (35/65) titrated to a target state entropy value of 40. Immediately prior to the start of surgical procedure, fentanyl 0.2 mg was administered. After that, the heart rate slowed from 68 to 56 beats/min, associated with mild decrease of arterial blood pressure (97/50 mm Hg). Atropine sulfate 0.5 mg was then administered. One minute later, the ECG rhythm on the monitor changed to third degree atrioventricular (AV) block with narrow-QRS complex, associated with marked hypotension (80/40 mm Hg).

INVESTIGATIONS

- ▶ Routine laboratory testing
- ▶ ECG
- ▶ Chest radiography
- ▶ Arterial blood gas analysis
- ▶ Serum electrolytes
- ▶ Cardiac enzymes
- ▶ 24h Holter ECG monitoring
- ▶ Pharmacological stress echocardiography

DIFFERENTIAL DIAGNOSIS

- ▶ Coronary ischaemia
- ▶ Myocardial infarction
- ▶ Electrolytes disorders
- ▶ Medications

TREATMENT

Ephedrine 10 mg was given to increase the arterial blood pressure. AV block persisted with a ventricular response rate of 40 bpm and was refractory to a second dose of atropine sulfate 0.5 mg. Waiting for transvenous pacing placement, a bolus of isoproterenol 0.02 mg was given. AV block was reverted to sinus rhythm with heart rate stabilised at 98 beats/min (figure 1). The patient became normotensive.

OUTCOME AND FOLLOW-UP

Serum electrolyte levels (sodium 138 mmol/L, chloride 106 mmol/L, potassium 4.4 mmol/L, calcium 1.22 mmol/L) and arterial blood gas analysis (PaO₂

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Figure 1 Graphic representation of the cardiovascular parameters in a patient with morbid obesity undergoing surgery. The red lines describe the trends of the systolic and diastolic arterial blood pressures (BP). The blue line represents the trend of the heart rate. The episode of severe bradycardia after the first atropine sulfate 0.5 mg administration corresponds to third degree atrioventricular block with narrow-QRS complex, associated with marked hypotension. After administering isoproterenol 0.02 mg, the third degree atrioventricular (AV) block reverted to sinus rhythm.

15 kPa, PaCO₂ 5.4 kPa, pH 7.4) were normal. Cardiac enzymes and ECG ruled out acute myocardial ischaemia and myocardial infarction. The surgical procedure went on as planned. After switching off desflurane administration and reversing the neuromuscular block with sugammadex, recovery from anaesthesia was uneventful. Postoperatively, a 12-lead ECG showed sinus rhythm with PR interval of 152 ms. A follow-up 24 h Holter ECG monitoring and pharmacological stress echocardiography did not show further episodes of bradyarrhythmia or signs of cardiac ischaemia. The patient was discharged from the hospital on the fifth postoperative day.

DISCUSSION

The temporal relationship with drug administration suggests that atropine sulfate was responsible for the AV block.⁴⁻⁶ Atropine sulfate is the first-line drug for acute symptomatic bradycardia and an initial dose of 0.5 mg is recommended.⁶ After intravenous administration, atropine sulfate distributes widely (apparent volume of distribution of 1–1.7 L/kg) and rapidly (distribution half-life of around 1 min) in tissues allowing a rapid increase in heart rate.⁷ However, the initial dose of 0.5 mg or lower may be inadequate for some patients, resulting in AV block.⁴⁻⁶ This suggests that the initial dose of atropine sulfate should be better titrated according to body weight (ie, 0.01 mg/kg) in normal weight patients.³ The concentration of atropine sulfate in tissues represents an important factor in order to avoid a paradoxical heart rate response. There is a relationship between the heart rate response and atropine sulfate concentration in the peripheral tissue compartment.⁷ After maternal administration of atropine sulfate 0.01 mg/kg, the fetal heart rate shows first an atropine-induced bradycardia associated with low fetal concentration, followed by a tachycardia produced by higher concentration.⁷ Bradyarrhythmia following low-dose atropine is caused by a paradoxical slowing in the sinoatrial node discharge rate. This is thought to be due to a central vagotonic effect of atropine that, at higher doses, is masked by muscarinic blockade at the sinoatrial node.⁸ The initial dose of 0.5 mg may not be sufficient to ensure an adequate peak concentration in peripheral tissues,

particularly in patients with MO, because of changes in body composition.¹⁻³ Lean body mass, fat mass, total blood volume, cardiac output, extracellular fluid volume and ratio of extracellular to intracellular fluid volume are increased in patients with MO.¹⁻³ Changes in regional blood flow and possible differences in the plasma protein concentration and the binding of drugs to plasma protein are also observed in patients with MO when compared with non-obese participants.¹⁻³ All these factors influence early drug distribution and dilution of anaesthetic drugs, and affect their peak concentration at tissue level.¹⁻³ This may represent the most likely explanation of the paradoxical heart rate response observed in our patient with MO after atropine sulfate administration. Several drugs used for the treatment of hypertension and cardiac diseases (ie, β -adrenergic blockers, calcium channel blockers) and anaesthetic drugs (ie, opioids, propofol) may have a negative chronotropic and/or dromotropic effect concurring to cause an adverse response to the administration of inadequate doses of atropine sulfate.^{9 10} Among anaesthetics, propofol has the potential to inhibit AV conduction in a concentration-dependent fashion.¹⁰ However, the concentrations needed for inhibition are much higher than the clinically achievable concentrations.¹⁰ Intraoperative myocardial ischaemia or infarction may concur to AV block.⁹ Even though possible, it seems unlikely in our patient, as the perioperative examinations ruled out ischaemic cardiac disease.

Dosing based on kilograms of total body weight (TBW) is valid for normal weight patients.¹⁻³ Obesity is associated with important physiological and anthropometric changes that alter the pharmacokinetic properties of most drugs.¹⁻³ In patients with MO, the fat tissue increases proportionally with TBW, but the lean body weight (LBW), which corresponds to TBW minus body fat weight, does not, and although the absolute value of LBW increases, the ratio of LBW/TBW decreases.¹⁻³ Many drugs need to be administered on the basis of LBW in patients with MO.¹⁻³ Atropine sulfate has a logarithmic octanol–water partitioning coefficient (log K_{ow}) of 1.83 and has pharmacokinetic properties similar to those of midazolam (log K_{ow} of 1.53) and alfentanil (log K_{ow} of 2.16) for which LBW represents the proper dosing scalar.^{2 3} The most relied on method for LBW calculating is Janmahasatian's formula: (LBW(male)) = $(9.27 \times 10^3 \times \text{TBW}) / (6.68 \times 10^3 + (216 \times \text{BMI}))$ (body mass index); LBW(female) = $(9.27 \times 10^3 \times \text{TBW}) / (8.78 \times 10^3 + (244 \times \text{BMI}))$.¹¹ So, since the LBW was 70 kg in our patient, atropine sulfate should have been administered at the dose of 0.7 mg, instead of 0.5 mg. Janmahasatian's formula is not rapidly applicable, and a simplified equation for rapid and accurate LBW determination in patients with obesity was recently derived (LBW(male) = $26 \times h^2$; LBW(female) = $22 \times h^2$).¹²

Learning points

- Morbid obesity (MO) alters drug dose requirement and time course of drug response. Consequently, incorrect dosing will increase the risk of complications.
- Atropine sulfate is a drug commonly used in anaesthesia. Its inadequate administration may be associated with paradoxical heart rate response.
- It is important to adopt lean body weight, calculated according to Janmahasatian's formula, to adjust the dose of atropine sulfate in order to avoid the risk of a paradoxical heart (bradycardia) response in patients with MO.

We would suggest adopting LBW to adjust the dose of atropine sulfate for the treatment of bradycardia in order to avoid the risk of a paradoxical heart rate response in patients with MO.

Competing interests None.

Patient consent Obtained.

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