Potential of pancuronium and vecuronium neuromuscular blockade by intravenous salbutamol

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Three doses of salbutamol 125 µg iv were given, over 3.5 hr, to a 28-yr-old healthy, previously non-asthmatic man during thiopentone-O₂/N₂O-isoflurane anaesthesia for treatment and prophylaxis of bronchospasm. Force of contraction of the adductor pollicis was measured before and after the last two injections. Initially, the patient was given pancuronium, 5 mg. Salbutamol, 125 µg iv, was given when T₁ blockade was 45%. Blockade increased to 66% over five minutes and returned to 45% after 18 min. Vecuronium was subsequently used to maintain relaxation. At the end of surgery, salbutamol was followed by an increase in T₁ blockade, from 66% to 86%, over five minutes which returned to 66% after ten minutes. It is concluded that intravenous salbutamol potentiates the neuromuscular blocking effect of nondepolarizing muscle relaxants.

Trois doses de salbutamol 125 µg iv sont administrées dans un intervalle de 3h30 à un patient de 28 ans jusque là en bonne santé pour traitement et prophylaxie d'un bronchospasme, au cours d'une anesthésie au thiopental, O₂/N₂O et isoflurane. Le patient n'a pas d'antécédents d'asthme. La force de contraction de l'adducteur du pouce est mesurée avant et après les deux dernières injections. Initialement, le patient avait reçu 5 mg de pancuronium. Du salbutamol à la dose de 125

µg iv est donné quand le bloc T₁ est de 45%. Le bloc augmente jusqu'à 66% en cinq minutes et revient à 45% après 18 min. Du vecuronium est ensuite utilisé pour maintenir la relaxation. À la fin de la chirurgie, le salbutamol a entraîné une augmentation, en cinq minutes, du bloc T₁ de 66% à 86%, lequel est revenu à 66% après dix minutes. On en conclut que le salbutamol iv renforce l'effet bloqueur neuromusculaire des myorelaxants non dépolarisants.

Nondepolarizing muscle relaxants may be potentiated by several drugs, including inhalational agents,^{1,2} local anaesthetics,³ antibiotics^{4,5} and calcium-channel blockers.⁶ We would like to report potentiation of pancuronium- and vecuronium-induced neuromuscular blockade by the intravenous administration of salbutamol, a β₂-agonist.

Case report

A 28-yr-old man, ASA physical status I with no history of asthma, weighing 75 kg, was scheduled for elective repair of an incisional hernia. Two years previously, he was involved in a motor vehicle accident which resulted in pelvic fractures and major abdominal trauma. Multiple intra-abdominal operations had left a large incisional hernia, extending from the xyphoid process to the symphysis pubis. He had smoked ten cigarettes a day for the last five years. The preoperative chest examination was unremarkable. He reported no known allergies and was taking no medications.

In the operating room, ECG, oxygen saturation and arterial blood pressure were monitored non-invasively. Before induction of anaesthesia, the patient was given d-tubocurarine 3 mg and fentanyl 150 µg iv. This was followed three minutes later by thiopentone, 500 mg iv. Tracheal intubation was facilitated by succinylcholine 200 mg. End-tidal CO₂, O₂ and isoflurane concentrations were monitored with a Datex Capnomac gas analyzer (Datex Instrumentarium Corp., Helsinki, Finland). The airway pressure at the mouth end of the endotracheal tube was monitored and displayed as a curve. In addition,

Key words

COMPLICATIONS: bronchospasm;

INTERACTIONS (DRUG): neuromuscular relaxants;

MONITORING: neuromuscular function;

NEUROMUSCULAR RELAXANTS: pancuronium, vecuronium;

PHARMACOLOGY: salbutamol.

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a digital readout of peak and mean airway pressures was available.

Immediately following intubation, manual ventilation with the reservoir bag was difficult. Mechanical ventilation was instituted and the tidal volume was set at 600 ml. Peak inspiratory pressures (PIP) were high (28 cm H₂O) and much greater than the plateau pressure (20 cm H₂O). Direct laryngoscopy was performed to verify the position of the tube and confirm the absence of mechanical obstruction. This manoeuvre was followed by a further increase in PIP to 40 cm H₂O. Bronchospasm was confirmed by auscultation of the chest. This episode was resolved within five minutes as anaesthesia was deepened by increasing the end-tidal isoflurane concentration. The PIP stabilized at 19 cm H₂O.

After recovery from succinylcholine, muscle relaxation was maintained using pancuronium, 5 mg *iv*. The Paragraph unit (Utah Medical Products) was used for neuromuscular monitoring. This new device contains a nerve stimulator, a movement-sensitive pad for muscle contraction and a screen displaying the train-of-four response as four separate bars. The train-of-four ratio is also computed numerically, but the device does not calculate first twitch height compared with control.

Twenty minutes after induction of anaesthesia and immediately after skin incision, the patient developed another episode of bronchospasm diagnosed by an increase in PIP from 19 to 40 cm H₂O. Salbutamol, 125 µg, *iv* was given and within a few minutes the PIP decreased to 19 cm H₂O. The inspired isoflurane concentration was not changed.

At the time of salbutamol injection, only the first twitch of the train-of-four (T₁) was visible on the Paragraph screen, and was palpable by tactile evaluation. Two minutes after salbutamol, T₁ disappeared from the Paragraph screen. Tactile evaluation of the train-of-four confirmed the absence of all four twitches. Ten minutes later, T₁ started to recover and reached its approximate height before salbutamol injection 20 min later. Salbutamol injection was also accompanied by a transient increase in heart rate from 80 to 115 min⁻¹ and an increase in blood pressure from 110/70 to 152/77 mmHg. No arrhythmia other than sinus tachycardia was observed.

To obtain better documentation of the salbutamol effect on neuromuscular blockade, it was then decided to use a Grass FT-10 force-displacement transducer to measure and record the force of contraction of the adductor pollicis. Forty minutes after the first injection, a second dose of 125 µg salbutamol was given *iv* to treat another episode of bronchospasm. At injection, T₁ blockade was 45% (using the maximum height of T₁ after reversal as a control) and train-of-four ratio was 14%. Two minutes later, there was a gradual increase in T₁ blockade to a

FIGURE 1 Pancuronium-induced neuromuscular blockade. Arrow marks salbutamol injection. Force of contraction of adductor pollicis in response to train-of-four stimulation of the ulnar nerve is displayed versus time. T₁ blockade increased from 45% to 66% over five minutes. This was followed by gradual recovery to its height before salbutamol injection after 18 min. Time scale is in minutes.

FIGURE 2 Vecuronium-induced neuromuscular blockade. Arrow marks salbutamol injection. Force of contraction of adductor pollicis in response to train-of-four stimulation of the ulnar nerve is displayed versus time. T₁ blockade increased from 66% to 86% over five minutes. This was followed by gradual recovery to its height before salbutamol injection after ten minutes. Time scale is in minutes.

maximum of 66% after five minutes. The train-of-four ratio decreased to 10%. This was followed by gradual recovery to its pre-salbutamol height after 18 min (Figure 1). Cardiovascular changes similar to those which followed the first dose were also observed. These were transient and required no treatment.

Because the patient was receiving a drug which potentiated neuromuscular blockade, it was decided to maintain relaxation with a shorter-acting muscle relaxant. Over the next 2.5 hr, muscle relaxation was maintained by five incremental doses of vecuronium, 1 mg. Eighteen minutes before reversal, and 22 min after the last dose of vecuronium, salbutamol, 125 µg *iv*, was given to prevent any bronchospasm which might accompany emergence from anaesthesia. At injection, T₁ blockade was 66% and train-of-four ratio was 12%. Five minutes later, T₁ blockade reached a maximum of 86%, and only three twitches were visible. This was followed by gradual recovery to the pre-salbutamol value after ten minutes (Figure 2).

The surgical procedure lasted for 3.5 hr. Since the resolution of the first episode of bronchospasm, the end-tidal isoflurane concentration had been maintained at 0.6% with no alteration during salbutamol treatment. Isoflurane administration was discontinued shortly before reversal. The residual blockade was reversed with glycopyrrolate 0.6 mg and neostigmine 2.5 mg, when T₁ blockade was 55% and T₄/T₁ was 16%. Both T₁ and

T_4/T_1 increased slowly, but ten minutes after reversal, T_4/T_1 was only 0.6. The patient was observed carefully in the recovery area. He had no more bronchospasm, showed no signs of residual weakness, and the rest of his hospitalization was unremarkable.

Discussion

This case report demonstrates that severe intraoperative bronchospasm can occur in non-asthmatic patients. Salbutamol *iv* is an effective treatment. However, it can potentiate the nondepolarizing muscle relaxants and delay recovery after reversal.

The two main lines of treatment of intraoperative bronchospasm are deepening the anaesthetic level (by intravenous or inhalational anaesthetics) and using bronchodilators.⁷ Deepening the anaesthetic level was tried first, but as bronchospasm recurred with skin incision, it was decided to use salbutamol.

Salbutamol is a synthetic sympathomimetic drug with predominant effect on β_2 receptors of the bronchial musculature. It can be administered orally, by inhalation or intravenously, for the symptomatic treatment of bronchospasm. The recommended intravenous dose is $4 \mu\text{g} \cdot \text{kg}^{-1}$ repeated after 15 min if necessary, to a maximum of 1,000 μg . Our patient received three bolus doses of 125 μg (less than $2 \mu\text{g} \cdot \text{kg}^{-1}$), for a total of 375 μg . Although salbutamol is as potent as isoproterenol on β_2 receptors, it is considerably less potent on β_1 receptors⁸ and thus cardiovascular effects do not occur unless it is administered intravenously or in large doses (more than 400 μg) by inhalation.⁹ When given intravenously, salbutamol stimulates β_1 receptors of the heart muscle leading to tachycardia and an increase in the systolic blood pressure. The effect on diastolic pressure is usually mild, due to the decrease in peripheral resistance secondary to β_2 receptor mediated arteriolar vasodilation.

The effect of catecholamines at the neuromuscular junction has been studied in animal preparations. Kuba found that adrenaline has two main effects at the neuromuscular junction of the rat diaphragm: a presynaptic stimulatory effect and a postsynaptic inhibitory effect.¹⁰ The presynaptic effect is mediated via α -receptors and is related to an increase in acetylcholine release. The postsynaptic effect is mediated via β_2 receptors, and is related to activation of the membrane Na^+/K^+ pump, which results in hyperpolarization of the postsynaptic membrane.¹¹ This effect can be blocked by specific β -receptor antagonists as well as by ouabain.¹² Bowman found that when adrenaline was administered during an infusion of d-tubocurarine, the α -stimulatory effect was short and was followed by the more prolonged β -effect, during which d-tubocurarine induced neuromuscular blockade was potentiated.¹¹ It appears that salbutamol has the same

neuromuscular effect in humans, except for the α -component.

Adrenaline and β_2 sympathomimetic agents have been found to have effects on muscle contractility. In cat soleus muscle, they increase the rate of relaxation, the end result being shortening of the contraction and a slightly reduced twitch height.^{11,13} This effect was probably of negligible importance in our patient. Total disappearance of T_1 (after the first administration of salbutamol) and of T_4 (after the last administration) suggests strongly a neuromuscular blocking effect, because increasing the rate of relaxation cannot explain the total disappearance of any of the train-of-four responses.

Recovery of neuromuscular function after neostigmine appeared to be slower than expected. Neostigmine, 2.5 mg ($33 \mu\text{g} \cdot \text{kg}^{-1}$), given at 45% T_1 recovery, produced only a T_4/T_1 ratio of 0.6 after ten minutes, in spite of a decreasing alveolar concentration of isoflurane. Using only marginally larger doses of neostigmine ($40 \mu\text{g} \cdot \text{kg}^{-1}$), Dernovoi *et al.*¹⁴ found a mean T_4/T_1 greater than 0.8, in the presence of more intense blockade (25% T_1 recovery instead of 45%) and greater isoflurane concentrations.

This case report illustrates the effect of acute administration of salbutamol on neuromuscular blockade. To the authors' knowledge, sensitivity of patients on chronic bronchodilator therapy to neuromuscular blocking drugs has not been documented. Such a study might be difficult to perform because most severe asthmatics take many different drugs, all of which may affect the neuromuscular junction. In addition, the neuromuscular effect of β_2 -agonists could be different with prolonged use.

We conclude that acute administration of salbutamol, a β_2 adrenoreceptor agonist, potentiates both pancuronium and vecuronium and is associated with prolonged recovery of the train-of-four after reversal of the residual neuromuscular blockade. This interaction between salbutamol and non-depolarizing muscle relaxants may be clinically important, especially if the β_2 -agonist is given shortly before emergence from anaesthesia.

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