Case Report

Donepezil: A cause of inadequate muscle relaxation and delayed neuromuscular recovery

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Abstract

A 74-year-old female with diabetes mellitus type II and Alzheimer's disease, taking donepezil for 4 months was operated for right modified radical mastectomy under general anesthesia. During the procedure a higher dose of non-depolarizing muscle relaxant was required than those recommended for her age yet the muscle relaxation was inadequate intra-operatively. Residual neuromuscular blockade persisted postoperatively, due to the cumulative effect of large doses of non-depolarizing muscle relaxant, needing post-operative ventilatory assistance. After ruling out other causes of resistance to non-depolarizing muscle relaxants, we concluded that acetylcholinesterase inhibitor donepezil was primarily responsible for inadequate muscle relaxation and delayed post-operative neuromuscular recovery.

Key words: Alzheimer's disease, donepezil, delayed neuromuscular recovery general anaesthesia, Geriatric, non depolarizing muscle relaxant

Introduction

The increase in life expectancy in human beings has lead to the increased prevalence of age-related disorders. Elderly patients are prone to systemic impairment and are generally on multidrug therapy, and thus present greater anesthetics challenges. Poly-pharmacy in elderly patients is one of the frequent and important factors in the incidences of drug interactions.[1] A thorough preoperative assessment and tailored anesthetic management is thus warranted. Anesthesiologists need to have in depth understanding of pharmacokinetics and dynamics as well as the possible adverse effect profile of the drugs from the other disciplines.[2] Perioperative monitoring must be individualized, considering the reduced safety and functional margins, in this special population and to safeguard the anesthetic outcomes.[2]

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Case Report

A 74-year-old woman, weighing 60 kg was posted for modified radical mastectomy under general anesthesia. She was detected to have Alzheimer's disease a year back and diabetes mellitus a month back. The patient was on oral metformin 500 mg BD and glimepride 2 mg OD therapy from 1 month and on donepezil 5 mg OD oral for 4 months. On examination, the patient apparently displayed slow mentation, fixed facial expression and sluggish motor movements. All laboratory investigations were within normal limits. Donepezil and the oral hypoglycemic agents were omitted on the morning of surgery.

All routine monitors were attached and intravenous access was secured, following which anesthesia was induced with intravenous administration of morphine 3 mg, propofol 100 mg, and rocuronium 0.6 mg/kg. The patient's lungs were ventilated for 3 min. On attempting endotracheal intubation, the patient's spontaneous respiratory efforts reappeared. Propofol 20 mg bolus and rocuronium 10 mg were supplemented intravenously to facilitate endotracheal intubation.

Anesthesia was maintained with isoflurane, O_2, and N_2O. 15 and 25 min after tracheal intubation, the patient's spontaneous efforts reappeared and rocuronium was administered intravenously. Assuming the possibility of poor efficacy of rocuronium, the muscle relaxant was switched

to vecuronium. However, the intraoperative requirement of muscle relaxant continued to remain higher than expected. On completion of the 2 h long surgical procedure and return of spontaneous respiratory efforts, residual neuromuscular blockade was reversed with intravenous administration of neostigmine 60 mcg/kg and glycopyrrolate 10 mcg/kg. However, the respiratory efforts remained clinically inadequate. After 15 min a supplemental dose of neostigmine 10 mcg/kg and glycopyrrolate 5 mcg/kg were administered but no improvement in the respiratory effort was evident. A rise in heart rate, blood pressure, and blood sugar levels was observed. The patient was put on titrating insulin infusion and was catheterized to monitor the urine output.

Postoperatively, serial blood gas monitoring showed gradually improving respiratory acidosis with manual ventilatory assistance. As neuromuscular monitoring was not available, clinical parameters of neuromuscular recovery were assessed. As the patient was conscious, following commands, moving her limbs purposefully, and had adequate respiratory efforts, the trachea was extubated. 5 to 10 min after extubation, the patient became tachypenic and was breathing shallow. Oxygen saturation (SpO_2) dropped to 85% at FiO_2 of 0.5 on venturi mask. The trachea was reintubated after administration of propofol 40 mg and succinylcholine 12.5 mg intravenous. The patient was shifted to ICU and put on pressure support mode of mechanical ventilation. The next morning the patient was conscious, well oriented and had adequate spontaneous respiration along with stable vital parameters. The patient was successfully weaned off the ventilator and trachea extubated. The patient was observed and O_2 by venturi mask was given. On the following day, the patient was shifted to surgical postoperative ward and subsequently discharged to home after 1 week.

Discussion

Prolonged neuromuscular paralysis is an undesirable but a known perioperative complication. The cause of prolonged paralysis can be drug over dosage, drug interactions, underlying medical conditions, co-morbidities, or altered pharmacokinetics and drug requirements in extremes of ages.

In the case reported, the 74-year-old patient did not have any significant medical history except for recent onset type II diabetes and Alzheimer's disease. The patient was taking oral metformin and glimepride for her diabetes and oral donepezil for Alzheimer's disease. She had no associated diabetic complication such as neuropathy. Both the oral hypoglycemic agents are not reported to have any significant interaction with donepezil or non-depolarizing muscle relaxants (NDMR). Donepezil is a reversible non-competitive inhibitor of acetyl cholinesterase with plasma half-life ($t_{1/2}$) of approximately 70 h.[3] Donepezil was possibly responsible for the seemingly inadequate muscle relaxation intra-operatively. The increased total dose requirement of NDMR may be explained by the increased availability of acetylcholine at neuromuscular junction. The prolonged neuromuscular blockade may have resulted from the residual effect of the large cumulative dose of NDMR.

Sanchez *et al*[4] reported prolonged neuromuscular blockade with succinylcholine followed by inadequate muscle relaxation with atracurium intra-operatively in a 75-year-old patient with Alzheimer's disease on donepezil therapy for 14 months. Baruah *et al*[5] also reported increased NDMR dose requirement with inadequate muscle relaxation intra-operatively in an elderly patient on donepezil. The above case reports are in concurrence with this case and support the possibility of donepezil being the agent responsible for the inadequate intra-operative and prolonged post-operative neuromuscular block.

More patients with such disorder, on acetyl cholinesterase inhibitor therapy, will require anesthesia in future and it is important that this interaction be highlighted. The manufacturer recommends omission of donepezil, at least 2–3 weeks prior to a scheduled surgical procedure[3]. This may not have a detrimental effect on the patient's overall cognitive function, as acetylcholine esterase inhibitor have no disease modifying action.[6] If the drug is continued till the day of surgery, one should anticipate the possibility of the residual neuromuscular blockade persisting for a prolonged duration.

References

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