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LETTER TO THE EDITOR

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What we need to know on timing principle of nondepolarizing muscle relaxant administration

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Sir,

the "timing principle" utilises administration of a single bolus dose of nondepolarizing muscle relaxant (NMR), followed by an induction drug at the onset of muscular weakness (1) was used in order to reduce the time for endotracheal intubation. Studied and extensively used in 1980s this method nowadays is somewhat forgotten, although still used. In the era of novel airway manipulation techniques, high dose rocuronium administration and sugammadex, is there still a place for timing principle during NMR administration in order to achieve a fast neuromuscular block?

The "timing principle" utilises administration of a single bolus dose of nondepolarizing muscle relaxant, followed by an induction drug at the onset of clinical weakness (1-4). Vecuronium, atracurium and rocuronium have all been used in this manner to decrease the effective onset time of NMR (1-4). This means administering muscle relaxant to an awake patient before induction of anaesthesia. What is the safest way to do this?

Rocuronium is known to cause pain during injection in 40-80 % of the patients (5). Intravenous (i.v.) injection of rocuronium is often associated with a localized withdrawal response even after loss of consciousness during induction of anaesthesia (6). Beside this unpleasant side effect, our concern is "can't ventilate, can't intubate" situations. Parmet et al. determined that difficult ventilation and intubation can occur in 1:1,000 anaesthetics, which was much higher than previously reported (7). In the case of "timing principle" administration of NMR, "can't ventilate, can't intubate" situation can be detrimental to the patient. Clinical value of bedside screening tests for predicting difficult intubation remains limited (8). "Timing principle" means that the intravenous anaesthetic agent is given only after the onset of clinical weakness. Nelson and colleagues, in their study, used a variation of the timing principle. They used rocuronium for intubation, in timing principle manner, but the time between the NMR and intravenous anaesthetic agent administration was fixed (20 seconds). None of the patients recollected of significant partial weakness just before the anaesthesia was induced (9).

Another unfavourable scenario is the loss of peripheral venous line after NMR has already been administered without induction agent. We witnessed a peripheral venous line displacement in a patient after induction of anaesthesia, which resolved

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favourably (the patient was intubated and another peripheral cannula was inserted without much delay).

As mentioned before, the role of the "timing principle" is to decrease the effective onset time of NMR. After the NMR is infused, the patient is still breathing spontaneously, still being preoxygenated, while NMR is starting its action.

Nowadays, sugammadex emerged as the first of a new class of selective binding agents. It was designed to rapidly encapsulate steroidal NMRs, specifically rocuronium, reversing even profound block (10-12). Although designed specifically for rocuronium, it was expected to reverse neuromuscular block when similar pharmacologic compound, such as vecuronium, is used (10). Suy and colleagues showed that sugammadex rapidly reverses rocuronium - or vecuronium -induced neuromuscular block at reappearance of the second muscle twitch (10).

When rocuronium is used in high doses (1,2 mg/kg), neuromuscular block can be reversed by a high dose of sugammadex (16 mg/kg) when given three minutes after rocuronium (11).

Nonetheless, when reversal of neuromuscular block by neostigmine or sugammadex is administered there is always a concern that "recurarization" will appear if the action of neostigmine or sugammadex wears off before all the remaining NMR will be metabolized.

There are reports on recurarization after sugammadex administration which was explained by the redistribution of rocuronium from peripheral tissues (12).

Furthermore, there is the issue of price of sugammadex, and its immediate availability in cases rocuronium is administered in high doses (13). This means that "timing principle" could still have a role in today anaesthetic practice.

For these reasons we are suggesting the following:

a) the "timing principle" should better be omitted, especially in patients suffering from anxiety or panic disorder and in those in which difficult airway is expected (difficult intubation or difficult ventilation);
b) if "timing principle" is used, a large peripheral cannula is checked with the infusion of at least 250 ml of crystalloid solution or two peripheral intravenous cannulas are positioned;
c) since the patient can experience muscle weakness before loss of consciousness, intravenous midazolam 2-4 mg should be administered before the administration of NMR;
d) when using rocuronium in "timing principle" manner lidocain (10-40 mg i.v.) should be used prior to rocuronium through the same cannula in order to minimize the pain during injection (5,6);
e) "timing principle" should be used only by experienced anaesthesia practitioners.

We personally sometimes use a modified technique using coinduction with midazolam 2-4 mg intravenously, intubating dose of vecuronium (0,1 mg/kg) followed after 20 seconds by an intravenous anaesthetic agent.

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