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Neuromuscular blockade in the elderly

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Abstract

The aim of the presented review is to highlight the clinical problem of postoperative residual curarization (PORC) following general anaesthesia in the elderly. Possible complications of PORC are described along with age-induced changes in pharmacokinetics of long and intermediate-acting neuromuscular blocking agents. This is intended to facilitate the selection and to promote appropriate intraoperative use of muscle relaxants in patients over the age of 65 years.

Key words: elderly patients; neuromuscular block, muscle relaxants; neuromuscular block, reversal; postoperative residual curarization

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Anaesthesiologists are regularly involved in the treatment of elderly patients due to the increasing life expectancy and rising number of surgeries in the aging population [1]. General anaesthesia comprises four crucial components: unconsciousness, analgesia, immobilization and haemodynamic stability [2]. Neuromuscular block serves the two latter purposes. As it maintains good surgical conditions as well as facilitating airway management, doses of both volatile and intravenous anaesthetics can be considerably reduced. This is of importance in patients over 65 years of age, particularly those older than 75. This group of patients is most susceptible to the adverse effects of anaesthetics [3], including decreased heart muscle contractility and hypotension, which pose a risk of cardiac and central nervous system ischaemia [4].

Unfortunately, advanced age is accompanied by an increasing risk of postoperative residual curarization (PORC) [5] which, along with intraoperative awareness [6], is one of the most clinically significant complications of the use of muscle relaxants. Residual blockade is currently defined by the train of four ratio (TOFR) < 0.9, although previous reports mentioned TOFR < 0.7. It may lead to severe respiratory complications in the post-operative period [7], and thus prolong hospitalization. Awareness of the specific issues of neuromuscular blocking agents use in the elderly is therefore crucial in daily anaesthesiological practice.

CLINICAL ASPECTS OF THE PHARMACOKINETICS OF NEUROMUSCULAR BLOCKING AGENTS IN THE ELDERLY

Doses of both steroid and benzylisoquinoline-derived non-depolarising muscle relaxants necessary to reach maximal block, i.e. 95% reduction of muscle response to a stimulus (effective $dose_{95}$, ED_{95}), do not vary significantly between elderly persons and younger subjects [8, 9]. This suggests that the physiology of the neuromuscular junction and the pharmacodynamics of neuromuscular blocking agents are not markedly altered in advanced age. It is the pharmacokinetics of these agents that is responsible for their altered clinical effects in the elderly.

Decreased cardiac output is accompanied by reduced skeletal muscle perfusion [3] and, consequently, one should expect a prolonged time to maximum blockade following drug administration [10, 11]. However, doses of muscle relaxants used for intubation are two to three, or even four times higher than ED_{95}. Not only does this decrease the time to maximum block which is taken advantage of in a rapid sequence induction with succinylcholine or rocuronium [12, 13], but it may also eliminate any differences in the onset of action between age groups. It has been proved that the onset of neuromuscular block induced with intubation doses of rocuronium, vecuronium and mivacurium in the elderly is not delayed when compared to younger patients [14–16].

Starting at the age of 40, the functional reserve of vital organs decreases by 1% every year [17]. The declining function of the liver and kidneys results in decreased clearance, increased half-life, and thus a longer duration of action of muscle relaxants (as expressed by the time to the recovery of muscle response to 25 % of the baseline) [18]. A prolonged duration of action becomes clinically significant in subjects over 75 years of age [19].

AMINOSTEROIDS

The use of pancuronium, a long-acting aminosteroid compound, which has both a prolonged clearance and duration of action in elderly patients [20], involves a risk of late recurarization. This is considered minimal when shorter acting aminosteroids are used. This is why pancuronium has been largely displaced by intermediate acting agents.

Rocuronium, which is currently the most commonly used neuromuscular blocking aminosteroid agent in the world, has a prolonged effect in the elderly. The earliest study concerning pharmacokinetics of this agent [21] showed that in patients over 70 the mean time to spontaneous recovery to 90% of the baseline muscle response measured at the adductor pollicis muscle to a single supramaximal stimulus was 74.4 minutes as compared to 47.9 in patients between 27–58 years of age. Yamamoto *et al.* [22] demonstrated that within 1–2 hours of administration of the last maintenance dose of rocuronium, or from the discontinuation of the infusion, TOFR values were < 0.9 in as many as 75% patients of 65–85 years of age, and only in 33% subjects aged 20–48. The relationship between the duration of neuromuscular blockade after an intubation dose of rocuronium and patient age is even more pronounced in cases of renal failure [23]. Patients over 70 years of age are also characterized by a longer duration of intense block after rocuronium is administered, i.e. mean time to response to a single stimulation preceded with tetanic stimulus, i.e. a post-tetanic count (PTC) = 1 [24].

Similarly to rocuronium, the duration of neuromuscular block after vecuronium is also significantly prolonged in elderly patients. Slavov *et al.* [25] observed that the mean duration of action was 36 and 50 minutes for patients under 50 and over 60 years of age, respectively. Moreover, the mean recovery index (RI), i.e. the time interval between muscle response recovery from 25 to 75% of the baseline, increases with age. Differences in RI values between younger and elder patients may be significant, ranging from 8 minutes in a study by McCarthy *et al.* [26] to over 30 minutes as reported by Lien *et al.* [27].

BENZYLISOQUINOLINE DERIVATIVES

Muscle relaxants of benzylisoquinoline structure (atracurium and cisatracurium) follow Hoffmann elimination, which is responsible for the breakup of almost 77% of the administered cisatracurium dose [28] and under 50% of the atracurium dose [29]. As a result, although the pharmacokinetics of these agents expressed by clearance and half-life [30, 31] may vary in different age groups, this seems to be of no clinical significance. Studies by Slavov [25] and Sooroshian [31], as well as Jin [32] and Ornstein [10], have demonstrated no difference in the duration of clinical effect of atracurium and cisatracurium between older (> 65 years) and younger patients.

When considering the safety of muscle relaxant use in elderly patients, the predictability of the agent's pharmacokinetics plays a major role, as it may strongly affect the variability of the duration of action between individuals. In this respect, benzylisoquinoline derivatives have an advantage over aminosteroids. Indeed, Arain *et al.* [33] defined variability in the duration of neuromuscular block as the difference between its duration in a respective patient and the mean duration in the entire patient group. The duration of a neuromuscular blockade following the administration of vecuronium and rocuronium in patients over 60 years of age demonstrated a greater variability compared to cisatracurium. This had a range of 102, 86 and 44 minutes for vecuronium, rocuronium and cisatracurium, respectively.

Puhringer *et al.* [34] analysed variability in the clinical duration of neuromuscular blockade following administration of a single dose of cisatracurium and vecuronium in two distinct age groups. The variability measured for cisatracurium and vecuronium was not significantly different within the two separate age groups (18–64 years and over 65 years). However, when the two groups were compared, it was revealed that it was greater for vecuronium than cisatracurium. Similarly, the duration of intensive block after a single intubation dose of rocuronium had a wider range in patients over 70 years of age than it did in younger subjects, between the ages of 20–60 [24].

Although interindividual variability of block duration in response to benzylisoquinoline muscle relaxants is thought to have no clinical significance, a study performed by Joomy *et al.* [35] seems to contradict this belief. The authors used a closed feedback loop devised to control cisatracurium administration with electromyographic response of the muscle. The system adjusted the rate of a continuous infusion of cisatracurium according to the registered relation of the first elicited response in the TOFR_sequence to its baseline value, which was supposed to remain within the pre-programmed range reflecting the desired depth of neuromuscular block. The reduction of the muscle response amplitude by 90% required higher doses of cisatracurium in patients aged 20–45 and 46–64 than in those older than 65. Recovery index values were higher in the two older age groups. These results indicate that in elderly patients a dose adjustment (with the dose calculated initially for ideal body

weight) might also be necessary when benzylisoquinoline derivatives are used so as to decrease the risk of prolonged clinical effect.

RESIDUAL NEUROMUSCULAR BLOCK AS A SIGNIFICANT CLINICAL PROBLEM OF THE POSTOPERATIVE PERIOD IN THE ELDERLY

Postoperative residual curarization (PORC), alternatively known as postoperative residual neuromuscular block (PRNMB), was initially defined as TOFR value < 0.7 [7]. This response magnitude as measured at the adductor pollicis muscle is, however, still accompanied by a suppressed respiratory response to hypoxia [36] and does not provide adequate recovery of muscle strength in the pharynx. It is a TOFR value of 0.9 that is required by the upper pharyngeal sphincter to regain its preoperative resting tone [37]. As a result, residual block is now defined as TOFR < 0.9.

Residual neuromuscular block has been reported not only after the administration of long acting [38] but also intermediate acting neuromuscular blocking agents, both aminosteroids and benzylisoquinoline derivatives [40]. PORC significantly increases the risk of severe postoperative respiratory complications including airway collapse, hypoxia, the need for reintubation, as well as pneumonia [7, 40, 41].

Since neuromuscular blockade lasts longer in elderly patients, one should also expect an increased incidence of residual curarization. In a study examining neuromuscular block induced with vecuronium, Baillard *et al.* [42] reported a higher median age in a group of patients with a detected PORC defined as TOFR < 0.7 compared to patients with greater TOFR values. This was confirmed by the results of two large prospective studies with residual blockade as the primary end-point in elderly patients after the administration of rocuronium [5, 43]. In a group of 415 patients Pietraszewski *et al.* [5] proved that if rocuronium is administered empirically and the blockade is not reversed by the end of anaesthesia, PORC (TOFR < 0.9) is commonplace, occurring in 89% of patients aged 65 and older with as many as 44% with TOFR < 0.7. In younger patients, TOFR values of < 0.9 and < 0.7 were observed in 77 and 20% of patients, respectively. They also had fewer hypoxic episodes in the postoperative period than the elderly. It should be noted that all patients recruited for the study were thought to have spontaneously recovered from neuromuscular block based on clinical criteria examined by the attending anaesthesiologist, such as the ability to raise one's head for more than 5 seconds and cough effectively.

Although reversal with neostigmine decreases the risk of residual blockade, its incidence still depends on the patient's age. After 50 μg kg^{-1} of neostigmine was administered in 300 subjects by the end of anaesthesia when the TOFR value reached at least 3, as reported by Murphy *et al.* [43], TOFR < 0.9 was detected in a postanaesthesia care unit (PACU) in 57.7% of patients aged 70 to 90 years old and in only 30% of those aged 18–50. In the same study, early postoperative complications were more common in the elderly and involved airway collapse and hypoxia requiring oxygen supplementation in the PACU. A higher incidence of postoperative atelectasis and pneumonia followed during further hospital stay (15.7% vs. 3% in younger patients). This is most probably attributable to the increased risk of aspiration. During a videoradiographic examination in patients aged over 65, significant swallowing disturbances with bolus penetration to the laryngeal inlet were identified when TOFR was below 0.9 [44].

CONCLUSION

Altered pharmacokinetics of neuromuscular blocking agents in elderly patients leads to prolonged duration of action of these drugs and delayed recovery from neuromuscular blockade compared to younger subjects after administration of doses calculated according to ideal body weight.

Although this mainly applies to aminosteroid compounds, benzylisoquinoline derivatives may also require dose adjustment to prevent residual blockade which is responsible for increased risk of postoperative complications in subjects over 65 years of age. Therefore, neuromuscular blockade in the elderly should be routinely monitored so that TOFR > 0.9 is maintained after anaesthesia.

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