CLINICAL OBSERVATIONS ON THE NEUROMUSCULAR BLOCKING ACTION OF ORG 9426, A NEW STERoidal NON-DEPOLARIZING AGENT

J. M. K. H. WIERDA, A. P. M. DE WIT, K. KUIZENGA AND S. AGOSTON

SUMMARY

The neuromuscular blocking effects of Org 9426, the 2-morpholino, 16-allyl-pyrrolidino derivative of the 3-desacetoxy analogue of vecuronium have been investigated in anaesthetized patients. Based on data from a pilot study, two doses, 250 and 500 μg kg⁻¹ (estimated as the ED₉₀ and 2 × ED₉₀, respectively) were chosen. Org 9426 appeared to be six to eight times less potent than vecuronium and showed a faster rate of development of neuromuscular block, with good to excellent intubation conditions within 60 s after administration of a dose of 500 μg kg⁻¹. The duration of action and the recovery index appeared to be similar to those of vecuronium. Side effects were not noted. Org 9426 may have advantages over existing non-depolarizing neuromuscular blocking agents with respect to rate of development of good intubating conditions, and is stable in aqueous solutions.

KEY WORDS

Neuromuscular relaxants: Org 9426, vecuronium. Intubation, tracheal.

Nearly 50 years after the introduction of curare into clinical practice, the search for better drugs led to clinical testing and development of a great number of non-depolarizing neuromuscular blocking agents. Recently developed blocking drugs are of intermediate duration and, to a major extent, free from side effects. However, even after intubating doses, onset times are relatively slow compared with that of suxamethonium. The clinical need for a "clean" non-depolarizing agent with a rapid onset time and a brief duration of neuromuscular blocking effect led to the development of Org 9426. In animal pharmacology, the onset time of Org 9426 appeared to be significantly faster than that of vecuronium [1]. Duration and recovery time were equal or slightly shorter than that of vecuronium. In addition, Org 9426 showed cardiovascular stability and it is stable in aqueous solution.

We have investigated the potency and the time course of action of Org 9426 at doses of 250 and 500 μg kg⁻¹ in anaesthetized patients.

METHODS AND RESULTS

We studied 22 ASA I and II patients (aged 18–50 yr) who gave informed consent to participate in the study which was approved by the local Medical Ethics Committee. Premedication consisted of midazolam 0.1–0.15 mg kg⁻¹ by mouth 1 h before induction of anaesthesia with thiopentone 4–6 mg kg⁻¹ and fentanyl 3–5 μg kg⁻¹. Maintenance was with a gas mixture of 65% nitrous oxide in oxygen and supplements of fentanyl and thiopentone. Tracheal intubation was performed immediately after induction following topical lignocaine (250-μg kg⁻¹ group) or 1 min after Org 9426 (500-μg kg⁻¹ group). Thereafter, carbon dioxide partial pressure was maintained at 4–4.6 kPa.

Mechanomyographic measurements were started after induction using the standard ulnar nerve–adductor pollicis muscle technique. Following stabilization of the twitch, patients received either 250 μg kg⁻¹ (n = 11) or 500 μg kg⁻¹
Table I. Degree of block and onset characteristics (mean (SD)) of Org 9426 compared with vecuronium in patients anaesthetized with an i.v. anaesthetic technique and 65% nitrous oxide in oxygen. Only six patients reached 75% block. ***Significant difference from vecuronium (P < 0.005, Wilcoxon's rank sum test)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (µg kg⁻¹)</th>
<th>n</th>
<th>Max. block</th>
<th>Lag time</th>
<th>75% block</th>
<th>Max. block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Org 9426</td>
<td>250</td>
<td>11</td>
<td>69 (22)</td>
<td>34 (11)***</td>
<td>94 (51)†</td>
<td>231 (59)</td>
</tr>
<tr>
<td>Org 9426</td>
<td>500</td>
<td>11</td>
<td>98 (03)</td>
<td>36 (14)***</td>
<td>68 (30)***</td>
<td>204 (72)</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>85</td>
<td>8</td>
<td>100 (00)</td>
<td>71 (34)</td>
<td>155 (78)</td>
<td>216 (96)</td>
</tr>
</tbody>
</table>

Comparison of these results with data for vecuronium from an identical study [3] suggests that Org 9426 has approximately 15% of the potency of vecuronium. Comparing the time course of action reveals close similarity between the two drugs [3]. The new compound has the major advantage that it offers good to excellent intubating conditions 1 min after administration of the estimated 2 x ED₉₀ dose. From the mean block of 69% in the 250-µg kg⁻¹ group, it may be concluded that a smaller dose may be used for intubation, as the ED₉₀ appeared to be within the range of 300–400 µg kg⁻¹. However, the intubating dose is probably close to 1.5 x ED₉₀.

The main change in the first phase of development of block is an intriguing finding which justifies further comparative studies of development of block. Possible explanations for this phenomenon include the relatively low neuromuscular blocking potency of this new compound, necessitating the use of a higher molecular load which results in an increase in both the initial concentration gradient and subsequently the transport of molecules of Org 9426 towards the biophase [4]. In addition, simultaneous and more pronounced inhibition of presynaptic nicotinic cholinoreceptors may be responsible for the rapid initial development of neuromuscular block after Org 9426 [5]. Pharmacokinetic factors, especially those governing the rate of distribution of drug to the biophase, may also be involved.

References

1. Muir AW, Houston J, Green KL, Marshall RJ, Bowman WC, Marshall IG. The effects of a new neuromuscular...