EFFECT OF DOXAPRAM ON NEOSTIGMINE EVOKED ANTAGONISM OF VECURONIUM NEUROMUSCULAR BLOCK

M. ORLOWSKI AND B. J. POLLARD

SUMMARY
We have examined the effect of doxapram on neostigmine-evoked antagonism of vecuronium neuromuscular block in a double-blind study in anaesthetized patients. Neuromuscular transmission was measured with a Datex Relaxograph. The mean time to recovery of the first contraction of the train-of-four (T1) from 25% to 75% was significantly longer in the presence of doxapram (138 (SEM 21) s; n = 23) than in its absence (95 (13) s; n = 29) (P = 0.014). The recovery of the train-of-four ratio was prolonged also in the presence of doxapram, although this difference was not statistically significant.

KEY WORDS

Doxapram is a potent respiratory stimulant which has been used in clinical practice for many years. The mode of action of doxapram is thought to be related to an increase in the sensitivity of both central and peripheral chemoreceptors [1-3].

An effect of doxapram at the neuromuscular junction has been demonstrated previously in vitro [4]. Doxapram alone augments neuromuscular transmission, probably by a presynaptic action while, in the presence of a partial non-depolarizing neuromuscular block, transmission is inhibited; probably a post-junctional effect.

The time when doxapram is most likely to be used clinically is at the end of an anaesthetic, to stimulate ventilation and to enhance recovery, which is also when recovery from neuromuscular transmission is awaited. It is possible that the addition of doxapram to the dynamically changing situation within the neuromuscular junction at this time might introduce unwanted complications. This study was designed therefore to examine the effect, if any, of doxapram on the evoked antagonism of neuromuscular transmission.

METHODS AND RESULTS
Following Ethics Committee approval, we studied 52 healthy adult patients (ASA I or II) undergoing elective gynaecological surgery. All patients were premedicated with lorazepam 2-3 mg orally 90 min before operation. On arrival in the anaesthetic room, five self-adhesive surface electrodes were attached to the patient's right hand and i.v. cannula inserted into the left forearm. All drugs were administered into a fast running infusion connected to this cannula. The electrodes were arranged so as to record the compound EMG from the adductor pollicis muscle produced by stimulation of the ulnar nerve at the wrist using a Relaxograph (Datex).

Anaesthesia was induced with fentanyl 100 μg and sufficient thiopentone to abolish the eyelash reflex. The patient was allowed to breathe 70% nitrous oxide in oxygen with 0.5% halothane via a Magill circuit. Ventilation was assisted if necessary and normocapnia maintained. The calibration sequence of the Relaxograph was activated and a control recording obtained. Vecuronium was then administered in an initial dose of 0.08 mg kg⁻¹. Further increments of vecuronium were given, if required, to maintain the first response of the train-of-four (T1) less than 10% throughout surgery. Anaesthesia was maintained with 70% nitrous oxide with 0.5% halothane and further increments of fentanyl as required. At the conclusion of surgery, T1 was allowed to recover spontaneously to 20% of control, at which point the antagonists were administered.

Patients were allocated randomly to two groups in a double-blind manner. Patients in group 1 received neostigmine 0.05 mg kg⁻¹ and glycopyrronium 0.01 mg kg⁻¹ followed immediately by doxapram 0.5 mg kg⁻¹. Patients in group 2 received neostigmine 0.05 mg kg⁻¹ and glycopyrronium 0.01 mg kg⁻¹ followed by normal saline. The doxapram or saline was given from previously prepared randomly coded ampoules.

Train-of-four was monitored at 20-s intervals throughout surgery and changed to 12-s intervals before antagonism of neuromuscular block. When T1 had recovered to a maximum and the train-of-four ratio (T4:T1) (TR) to > 0.75, anaesthesia was discontinued and the trachea extubated when the patient was awake.

The time of recovery of T1 from 25% to 75% of control and of T4:T1 from 0.25 to 0.75 were measured. The groups were compared using the Mann–Whitney U test.

The two groups did not differ significantly in mean body weight, duration of operation or total dose of vecuronium (table I).

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**Table I.** Mean (SEM) patient data, dose of vecuronium, duration of surgery and times of recovery from neuromuscular block with and without doxapram. *P < 0.05 compared with control.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Doxapram)</th>
<th>Group 2 (Control)</th>
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<tbody>
<tr>
<td>n</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62 (3.4)</td>
<td>60 (2.3)</td>
</tr>
<tr>
<td>Vecuronium total dose (mg)</td>
<td>7.0 (0.8)</td>
<td>6.0 (0.4)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>46 (5)</td>
<td>40 (4)</td>
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<tr>
<td>Recovery time (s)</td>
<td></td>
<td></td>
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<tr>
<td>T1 25% to 75%</td>
<td>138 (21)*</td>
<td>95 (13)</td>
</tr>
<tr>
<td>T4:T1 0.25 to 0.75</td>
<td>252 (25)</td>
<td>221 (22)</td>
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The mean time for recovery from 25% to 75% was greater in the doxapram group (138 s) than in the control group (95 s) \((P = 0.014)\). Recovery of T4:T1 from 0.25 to 0.75 was also greater in the doxapram group (252 s) compared with the control group (221 s), but this difference was not significant (table I).

**COMMENT**

This study suggests that the presence of doxapram retards neostigmine-induced antagonism of a vecuronium neuromuscular block. The antagonism of a neuromuscular block is complex and there are several possible ways in which doxapram could impede the process. A direct effect on the motor neurons to reduce their rate of firing seems unlikely. A previous in vitro study demonstrated no direct effect of doxapram on muscle in concentrations greater than would have been achieved in this study [4]. It would seem most likely, therefore, that the observed effect of doxapram is within the neuromuscular junction. This is reinforced by previous work which confirmed the existence of an inhibitory effect of doxapram on a partially blocked neuromuscular junction [4]. The study concluded that the action was taking place at the postjunctional receptor site, although the precise action at the receptor remains to be determined.

Vercuronium is 30% bound to plasma proteins [5]. It is possible that doxapram might displace vecuronium from extrajunctional binding sites, an action which would increase the unbound fraction of vecuronium. In view of the dependence of neuromuscular block on the free concentration of vecuronium at the neuromuscular junction, the extent of block would effectively increase, and this might be reflected as a delay in antagonism.

An interaction between doxapram and either neostigmine or cholinesterase has to be considered also. If doxapram were to inhibit the action of cholinesterase, or to reduce the ability of neostigmine to combine with or to inactivate cholinesterase, antagonism of neuromuscular block might be prolonged. No effect of doxapram was found on the activity of the cholinesterase from rat diaphragms in vitro [4]. However, a chemical interaction with neostigmine, or an effect on the interaction between neostigmine and cholinesterase cannot be excluded.

**REFERENCES**