SHORT COMMUNICATIONS

EFFECT OF DOXAPRAM ON THE RATE OF RECOVERY FROM ATRACURIUM AND VECURONIUM NEUROMUSCULAR BLOCK

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SUMMARY

We have studied the effect of doxapram on the rates of spontaneous and neostigmine-induced recovery from neuromuscular block with atracurium and vecuronium, by measurement of the time to recovery of T1 (first twitch in the train-of-four) from 25 to 75% of control (recovery index, RI). After each neuromuscular blocking drug, RI was measured without administering either doxapram or neostigmine (control group), or after administration of doxapram 1 mg kg⁻¹, neostigmine 50 μg kg⁻¹ or a combination of doxapram and neostigmine, in groups of 10 patients. RI was significantly longer after vecuronium in the presence of doxapram compared with control (20.1 min vs 14.6 min). There was no significant difference in the RI after atracurium in the presence of doxapram compared with control (12.5 min vs 11.8 min) or when neostigmine was administered with or without doxapram (2.4 min vs 2.4 min, respectively after vecuronium; 3.3 min vs 2.9 min, respectively, after atracurium).

KEY WORDS


The analeptic agent, doxapram, is often used at the end of anaesthesia to stimulate ventilation and accelerate recovery from the effects of volatile anaesthetic agents without antagonizing analgesia [1, 2]. A recent experimental study has demonstrated that it may enhance a partial neuromuscular block by agents such as tubocurarine [3]. This is clinically important as doxapram is often administered when residual neuromuscular block may still be present. The purpose of this study was to examine the effect of doxapram on neuromuscular transmission by measuring the recovery index in patients given vecuronium or atracurium—the two neuromuscular blockers which currently are in most common use [4].

METHODS AND RESULTS

We studied 80 adult patients aged 18–70 yr (ASA I or II) with their informed consent and the approval of the Regional Medical Ethics Committee. Patients with obesity, renal or hepatic dysfunction, or receiving any drugs known to interact with neuromuscular blocking agents were excluded from study. All patients were premedicated with oral diazepam 10 mg 60–90 min before surgery. Anaesthesia was induced with fentanyl 1–2 μg kg⁻¹ and thiopentone 3–5 mg kg⁻¹ and maintained with 70% nitrous oxide and 0.5% halothane in oxygen; increments of fentanyl 0.5–1.0 μg kg⁻¹ were administered as required. ECG, non-invasive arterial pressure, temperature, end-tidal carbon dioxide concentration and oxygen saturation were monitored. Ventilation was adjusted to an end-tidal carbon dioxide concentration of 4.5–5.5.

The ulnar nerve was stimulated percutaneously at the wrist after induction of anaesthesia with supramaximal stimuli of 0.2 ms duration, in a train-of-four (TOF) mode at 2 Hz every 10 s, and the resultant force of contraction of the adductor pollicis muscle measured and recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Ltd). When control responses had stabilized, 40 patients received vecuronium 80 μg kg⁻¹ and the other 40 atracurium 450 μg kg⁻¹ (approximately 2 x ED₉₅ doses). Additional increments of the agent were given at T1 (first response in the TOF) 20% of control according to the duration of surgery. Within each group of 40, when the T1 had recovered to 25% of control, groups of 10 patients received doxapram 1 mg kg⁻¹ (group I), neostigmine 50 μg kg⁻¹ and doxapram 1 mg kg⁻¹ (group II), neostigmine 50 μg kg⁻¹ (group III) or saline (group IV, control group). Patients receiving neostigmine also received glycopyrronium 10 μg kg⁻¹. The allocation to these groups and to neuromuscular blocking drug was randomized. The time taken for T1 to recover from 25 to 75% of control (recovery index, RI) was recorded and used to measure the speed of recovery. TOF ratios at T1 75% were recorded also. The study was discontinued at this stage and the patient managed appropriately.

With each blocking drug, the groups receiving neostigmine were compared with each other, as were the groups who did not receive neostigmine. The results were subjected to analysis of variance and the Tukey HSD modification of the analysis of variance to determine statistical significance.

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The patients in the eight groups were comparable in physical characteristics (table I). RI in the vecuronium group which received doxapram was significantly greater ($P < 0.05$) compared with the control (saline) group (20.1 min vs 14.6 min; mean difference 5.5 min, 95% confidence limits of the difference 0.26-10.74 min). RI was not significantly different between groups to whom neostigmine was administered (2.4 min in both groups). After atracurium, RI was not significantly different between groups receiving neostigmine (3.3 min and 2.9 min) or in spontaneously recovering groups with or without doxapram (12.5 min vs 11.8 min). There was no significant difference in the TOF ratios at T1 75% in both neuromuscular blocker groups with or without doxapram, although the ratios were significantly greater in the groups given neostigmine (table I).

COMMENT

The results of this study suggest that a single dose of doxapram 1 mg kg$^{-1}$ significantly prolonged spontaneous recovery from neuromuscular block induced by vecuronium but not that with atracurium. Recovery induced by neostigmine was not affected in the present study, although it has been observed elsewhere [5].

Pollard, Randall and Pleuvry [3] suggested from an in vitro study that doxapram enhanced the neuromuscular block produced by agents with relatively greater presynaptic effect. The results of the present study do not support this contention, as vecuronium has been reported to have a relatively lesser presynaptic effect than atracurium during the onset of block [6]. In any case, there is no evidence to suggest that vecuronium has greater presynaptic effect than atracurium. Doxapram may be affecting the uptake of vecuronium by the liver, but this is speculative. However, if this were the reason then atracurium, which is less dependent upon liver for termination of its action, would be less affected, as in the present study. At present the reason for the interaction between doxapram and vecuronium remains unclear.

Our findings differ from those of Pollard and Orlowski [5], who demonstrated that antagonism of vecuronium-induced neuromuscular block by neostigmine was retarded in the presence of a single bolus dose of doxapram 0.5 mg kg$^{-1}$. There was no such inhibition in the presence of neostigmine in the present study, but this may be the result of the use of a larger dose of doxapram in our study. A direct comparison cannot be made with the former study, as it did not assess the effect of doxapram on the rate of spontaneous recovery from vecuronium block.

In summary, a single dose of doxapram 1 mg kg$^{-1}$ prolonged the rate of spontaneous recovery from a vecuronium-, but not atracurium-induced neuromuscular block. Neostigmine-induced recovery was unaffected. Although the differences in the present study were relatively small, they may be clinically important in situations in which neuromuscular block is not adequately antagonized or when larger doses of vecuronium are used.

references