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Atropine-neostigmine mixture: a dose-response study

The dose-response relationship and the doses of atropine required to prevent neostigmine from lowering heart rates below baseline in 50 per cent (ED50) and 95 per cent (ED95) of patients after antagonism of pancuronium-induced neuromuscular blockade were determined in 70 patients with neostigmine-atropine mixtures. Neostigmine $0.04 \text{ mg} \cdot \text{kg}^{-1}$ (group A, $n = 35$) or $0.06 \text{ mg} \cdot \text{kg}^{-1}$ (group B, $n = 35$) was randomly mixed with one of seven doses of atropine (ranging from 0.014 to $0.04 \text{ mg} \cdot \text{kg}^{-1}$) in group A and from 0.02 to $0.04 \text{ mg} \cdot \text{kg}^{-1}$ in group B), with dose-response curves for atropine being constructed for both groups 5 and 10 min after injection of the mixture. These dose-response curves were found to be parallel in both groups. The calculated ED50 and ED95 values of atropine were similar in both groups. The estimated ED50 doses of atropine in groups A and B at 5 min were 0.031 and $0.033 \text{ mg} \cdot \text{kg}^{-1}$ respectively, and at 10 min the ED50 doses were 0.037 and $0.037 \text{ mg} \cdot \text{kg}^{-1}$ respectively. The calculated ED95 doses of atropine in groups A and B at 5 min were 0.05 and $0.046 \text{ mg} \cdot \text{kg}^{-1}$, and at 10 min the ED95 doses were also similar, being 0.06 and $0.055 \text{ mg} \cdot \text{kg}^{-1}$ respectively. Under the conditions employed in this study it would seem that in order to prevent late reductions in heart rates, the appropriate doses of atropine when used with neostigmine should be greater than that commonly used.

Keywords:

ANTAGONIST, NEUROMUSCULAR RELAXANTS: neostigmine; HEART: pulse rate; PARASYMPATHETIC NERVOUS SYSTEM: atropine.

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Of anticholinergic agents, atropine is probably the most frequently used drug in anaesthesia. Atropine is used to antagonize the cholinergic effects of neostigmine during the reversal of non-depolarizing neuromuscular blocking drugs. Considerable differences of opinion exist concerning the dose of atropine required to prevent the bradycardic response of neostigmine.¹⁻³ Different ratios of atropine to neostigmine doses (ranging from 1:2 to 1:3.3) have been recommended by different investigators.¹⁻³ While Gravenstein and Perkins⁴ concluded that about twice the dose of atropine (i.e., 2:1 ratio) was required to prevent neostigmine from lowering heart rates below baseline in fit volunteers. Such conflicting opinions can give no useful evidence to the most appropriate dose of atropine required to prevent bradycardia in 50 per cent (ED50) or 95 per cent (ED95) of patients during antagonism of residual neuromuscular blockade with neostigmine. Further, the dose-response relationship has not been evaluated for atropine during antagonism of neuromuscular blockade with higher doses of neostigmine ($0.06 \text{ mg} \cdot \text{kg}^{-1}$).

Therefore, we compared the atropine requirements of two doses of neostigmine (0.04 and $0.06 \text{ mg} \cdot \text{kg}^{-1}$) in terms of changes in heart rate, and evaluated the dose-effect relation for atropine at various time intervals. We also estimated the dose of atropine required to prevent bradycardia in 50 and 95 per cent of the patients, i.e., ED50 and ED95 respectively, with the two doses of neostigmine.

Methods

After institutional approval, 70 ASA physical status I or II patients undergoing elective surgical procedures were studied. All patients were free of cardiac, neuromuscular, renal or hepatic disease. All had normal preoperative ECGs and normal laboratory values for serum electrolytes, BUN, creatinine, SGOT, and alkaline phosphatase. Informed consent was obtained. All patients were premedicated with diazepam 10-15 mg PO 90 minutes preoperatively.

An IV infusion of lactated Ringer's solution in five per cent dextrose was started before induction of anaesthesia. The ECG (lead II) and nasopharyngeal temperature were monitored continuously. Blood pressure was measured by

an electronic oscillotonometer (Dinamap). In all patients, anaesthesia was induced with fentanyl $2 \mu\text{g} \cdot \text{kg}^{-1}$ and thiopentone $5 \text{ mg} \cdot \text{kg}^{-1}$, and was maintained with 70 per cent nitrous oxide in oxygen and halothane (0.5–1 per cent inspired). Pancuronium $0.1 \text{ mg} \cdot \text{kg}^{-1}$ was administered to provide neuromuscular blockade. Ventilation was adjusted to maintain normocapnia and end-tidal CO_2 was monitored using a Datex infra-red CO_2 analyzer.

Neuromuscular activity was assessed by observation of thumb adduction, using a Bard peripheral nerve stimulator applying supramaximal stimuli to the ulnar nerve at the wrist. Observation of thumb adduction was made easier by fixing the medial four fingers with adhesive tape to an armboard and the arm abducted to approximately 90° . Train-of-four (TOF) stimulation was used throughout the study. At the conclusion of surgery patients were assigned randomly to one of two groups (group A, $n = 35$ and group B, $n = 35$). When recovery of two of the four responses in the TOF occurred, the neuromuscular blockade was antagonized with neostigmine $0.04 \text{ mg} \cdot \text{kg}^{-1}$ or $0.06 \text{ mg} \cdot \text{kg}^{-1}$ in groups A and B respectively. Neostigmine was randomly mixed with one of the seven doses of atropine in each group as shown in Tables I and II. Five patients were studied at each dose of atropine. The neostigmine-atropine mixture was administered as a single bolus injection. Control heart rate was the rate prior to the administration of the drug mixture. Heart rate (as measured by ECG) was recorded at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 and 30 min following antagonist administration. Patients continued to inhale nitrous oxide in oxygen and 0.5–1 per cent halothane for ten minutes after the administration of the antagonist. Patient stimulation was avoided during this period. After the measurements at the tenth minute, nitrous oxide and halothane were discontinued and 100 per cent oxygen was given. With the return of all responses of TOF stimulation and the presence of a sustained muscle contraction in response to a tetanic stimulus (50 Hz for 5 sec), the tracheal tube was removed. Further assessment of patients was carried out in the Recovery Room for 60 min, using clinical criteria such as ability to open eyes, cough and sustain a head lift. The ECGs were examined in detail for changes in heart rate and rhythm.

Data processing

Statistical analyses were performed by the BMDP (1987) statistical package. In an attempt to predict variables important in contributing to the changes in the heart rate, multiple regression (all possible subset regression analysis) was used. Percentage change in the heart rate and difference in the heart rate from control values were each regressed on the independent variables (age, body weight, control heart rate, and the dose of atropine). The same

procedures were repeated using log dose instead of the dose. The "best" subset model was selected using Mallows' coefficient (C_p) and R-square criteria.⁵ Per cent change in heart rate and the set of independent variables containing the log dose was found to be the best fitted model between 5 and 10 min intervals in both groups. In all of these models ANOVA for linearity was highly significant ($P < 0.002$), and at the same time the only significant factor contributing to the response was the log dose. Hence, we used a simple regression analysis to determine the dose-response relationship (percentage change in heart rate from the control value versus log dose) in both groups at 5 and 10 min. Regression lines in both groups were compared using analysis of co-variance.⁶ Then we tested for the difference between slopes of the two lines using analysis of co-variance. This difference was found to be insignificant ($P > 0.88$) at 5 and 10 min. Also, the test of difference between elevations was not significant ($P = 0.79$).

To compare the potency of atropine between the two groups, we calculated the ED50 and ED95 doses of atropine at 5 and 10 min. As defined, this is a quantal rather than a graded response, since the specified effect (the presence or absence of an increase in heart rate from the control value following the administration of the antagonistic mixture) is either present or absent (i.e., an all or none response). Patients were considered to have a positive or negative response based on this criterion. The ED50 and ED95 were calculated by fitting the number of patients with positive response at each dose level of atropine to a logit model⁷ using PCNONLIN.⁸

Using analysis of variance, we compared mean age and body weight among subgroups. Changes in heart rate in each subgroup were analyzed by analysis of variance for repeated measures. If the hypothesis was rejected, individual comparisons were performed by Bonferroni adjusted paired *t* test. The incidence of dysrhythmia was analyzed using Fisher's Exact Test. For all statistical comparisons, differences were considered significant when $P < 0.05$.

Results

All results were expressed as means $\pm$ SEM. There were no significant differences among the subgroups regarding patients' age, sex or weight. The mean age was 28.6 ± 3 and 26 ± 2.5 years, and mean body weight 63.6 ± 4.3 and 62.4 ± 4.3 kg in groups A and B, respectively. The male/female ratio was 20/15 and 21/14 in groups A and B, respectively.

Changes in heart rate after administration of the mixtures are shown in Tables I and II. The administration of atropine produced a significant increase in heart rate at one minute in all but subgroup B-1. Subsequently, the

TABLE I Atropine dose, control heart rate and heart rate following antagonism of pancuronium induced neuromuscular blockade in group A with a mixture of neostigmine $0.04 \text{ mg} \cdot \text{kg}^{-1}$ and different doses of atropine as shown in the table. Mean values ($\pm$ SEM) are shown

Group A <i>n</i> = 35	Atropine dose $\text{mg} \cdot \text{kg}^{-1}$	Control heart rate $\text{beat} \cdot \text{min}^{-1}$	Heart rate after reversal															
			1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min	15 min	20 min	25 min	30 min		
A-1 (<i>n</i> = 5)	0.014	91.6 (3.5)	105* (3.6)	89.8 (6.3)	79.4 (5.6)	77* (3.9)	75* (3.6)	74* (3.2)	72* (3.9)	73.6* (4.1)	72.6* (4.5)	69.6* (5.3)	82.8 (7.4)	90 (2)	94 (1.8)	95 (2.9)		
A-2 (<i>n</i> = 5)	0.0155	82.4 (3.5)	105.6* (0.6)	84 (4.3)	72 (2.1)	66.8* (3.8)	64.8* (3.7)	62* (2.7)	59.4* (2.1)	58.2* (2.2)	57.2* (2)	57.6* (2.2)	73.4 (7.1)	92.6 (9.1)	85.4 (8.7)	82.2 (9.9)		
A-3 (<i>n</i> = 5)	0.017	84.6 (6.4)	105.8* (5.4)	85.2 (8.6)	76 (8.9)	71.2 (8.5)	69 (7.3)	68.2 (6.9)	66.8 (6.2)	66* (5.7)	65.2* (4.9)	64.4* (5.1)	76.2 (3.8)	79.6 (4)	86 (3.4)	91 (5.3)		
A-4 (<i>n</i> = 5)	0.02	92.4 (8.8)	108.2* (8.2)	93 (7)	79 (4.7)	70.8* (3.7)	66* (2.5)	63.8* (2.6)	63.2* (2.5)	62.8* (2.2)	62.6* (2.1)	61.6* (2)	85 (8.9)	84.2 (5.1)	85.6 (3.6)	84.4 (5.4)		
A-5 (<i>n</i> = 5)	0.0215	83 (2.5)	103.2* (2.6)	91.8 (4.3)	82.4 (6.9)	78 (8)	75.8 (8.4)	73.8 (8.2)	72.8 (8.4)	71.4 (8.5)	69.6 (6.9)	70.4 (7.5)	89.8 (8.1)	69.8 (4.7)	68.8 (4.5)	74.2 (5.1)		
A-6 (<i>n</i> = 5)	0.03	78.6 (2.8)	96.4* (2.9)	85.2 (3.2)	76.4 (4.1)	72.8 (4.8)	71.2 (4.6)	70 (4.1)	69.6 (4.1)	69 (3.7)	68.4 (3.6)	67.6 (3.5)	83.2 (4.1)	81.8 (5.2)	78.6 (3.2)	83.6 (6.3)		
A-7 (<i>n</i> = 5)	0.04	83.8 (6)	115.4* (4.2)	102.8* (4.5)	93 (4.5)	89.2 (3.3)	86.8 (3.1)	85 (3.6)	84.4 (3.5)	81.4 (3.7)	80.2 (4.3)	80.2 (2.8)	98* (3.5)	97* (4.2)	93.6 (5.5)	86.2 (1.4)		

*Different from control ($P < 0.05$).

TABLE II Atropine dose, control heart rate and heart rate following antagonism of pancuronium-induced neuromuscular blockade in group B with a mixture of neostigmine $0.06 \text{ mg} \cdot \text{kg}^{-1}$ and different doses of atropine as shown in the table. Mean values ($\pm$ SEM) are shown

Group B <i>n</i> = 35	Atropine dose $\text{mg} \cdot \text{kg}^{-1}$	Control heart rate $\text{beat} \cdot \text{min}^{-1}$	Heart rate after reversal															
			1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min	15 min	20 min	25 min	30 min		
B-1 (<i>n</i> = 5)	0.02	82.8 (4.3)	95.2 (6)	70.4 (2.1)	64* (3.5)	62.6* (3.3)	62.8* (3.6)	63* (3.3)	62.6* (3.4)	62.2* (3.4)	61.4* (3.3)	60.8* (3)	70.8 (9.1)	78.2 (8.1)	75.6 (6.7)	75.4 (6.3)		
B-2 (<i>n</i> = 5)	0.0215	80.6 (4.9)	97* (3.1)	74.8 (3.8)	71.4 (6.5)	70.8 (6.8)	71 (5.2)	71 (6.5)	71.2 (7)	69.8 (5.4)	65.4 (3.7)	66.6 (3.7)	78 (13)	86.8 (9.2)	84.4 (9.3)	92 (12.8)		
B-3 (<i>n</i> = 5)	0.023	83.2 (7)	104.8* (9.4)	83 (6.9)	70.6 (5.4)	67.4 (6.2)	66.4 (6)	65.8 (6.2)	64* (6.4)	63.2* (5.4)	63.6* (5.2)	61.4* (5)	76 (8.2)	79.2 (4.6)	75.4 (5)	78.8 (3.8)		
B-4 (<i>n</i> = 5)	0.025	74.6 (4)	98.2* (5.9)	75.8 (6.2)	65 (4.3)	63.6 (5.4)	62.4 (5.3)	62 (5.3)	61.2 (4.7)	61.8 (4.9)	61 (5)	60 (5)	84.8 (15.6)	85 (7.5)	84.2 (9.9)	78.8 (5.8)		
B-5 (<i>n</i> = 5)	0.03	73 (3.7)	95.2* (3.9)	79.4 (5.5)	70.2 (6.3)	65.8 (5.1)	61.8 (5.6)	61.6 (4.1)	61.2 (3.6)	60.6 (3.4)	60 (2.7)	59.6 (2.5)	69.2 (10.1)	73.8 (4.8)	76.2 (5.2)	79.6 (5.3)		
B-6 (<i>n</i> = 5)	0.035	82.4 (4.9)	106.4* (7.2)	86.4 (7.5)	88.6 (10)	84 (8.9)	81.4 (8.3)	78.4 (7.3)	77 (6.2)	75.4 (5.4)	76.2 (4.3)	75.4 (3.9)	71.8 (3.4)	84 (6.6)	91 (4.7)	85.8 (6.3)		
B-7 (<i>n</i> = 5)	0.04	83.6 (6.6)	106* (12.4)	101.2* (6.3)	89.6 (5.8)	86.2 (4.8)	83.2 (4.3)	81 (3.7)	80 (3.7)	78 (4.5)	76.2 (4.6)	76.4 (4.6)	80.8 (6.8)	99.6 (6.3)	89.2 (6.2)	85.2 (5.1)		

*Different from control ($P < 0.05$).

heart rate decreased significantly in the subgroups A-1 to A-4, B-1 and B-3 (Tables I and II). The maximum mean decreases of heart rates occurred at 9–10 min in both groups. The increase in heart rate in both groups at 15–30 min coincided with awakening of the patient and extubation of the trachea.

There was a significant linear correlation between the log dose of atropine and the changes in heart rate (expressed as a percentage from preinjection control values).

The sample regression equations of the lines in group A

at 5 and 10 min, and the P value for the slopes were, respectively:

$$Y = 74.42 + 52.873 \times, \quad (P < 0.001), \text{ and}$$

$$Y = 66.94 + 52.112 \times, \quad (P < 0.001).$$

In group B, the equations of the regression lines at 5 and 10 min, and the P value for the slopes were, respectively:

$$Y = 101.78 + 72.661 \times, \quad (P = 0.002), \text{ and}$$

$$Y = 76.35 + 59.692 \times, \quad (P < 0.001).$$

FIGURE

The regression lines for both groups at 5 and 10 min are in the Figure. The test for significance of difference between slopes indicated that the regression lines did not deviate from parallelism ($P > 0.88$) and did not differ in position ($P = 0.79$).

The ED50 and ED95 values of atropine following administration of atropine-neostigmine mixtures in both groups are shown in Table III. The ED50 and ED95 of atropine when calculated at five minutes, were similar to that of ten minutes in each group. Although patients in group B received a higher dose of neostigmine ($0.06 \text{ mg} \cdot \text{kg}^{-1}$) compared with those in group A ($0.04 \text{ mg} \cdot \text{kg}^{-1}$), the calculated ED50 and ED95 doses of atropine were similar in both groups.

Dysrhythmias were observed in nine patients in group A and six patients in group B. The type of dysrhythmias encountered are summarized in Table IV. There was no significant difference in the incidence of dysrhythmias between the two groups ($P = 0.28$). Dysrhythmias resolved spontaneously without any treatment in all but one patient in group B who required an additional dose of atropine (0.5 mg) at the 11th minute.

Discussion

Many investigators recommended that about one-half weight unit or less of atropine suffices to block the undesirable effects of one weight unit of neostigmine.¹⁻³ It is surprising that bradycardia was frequently observed in patients following administration of doses in these ratios.¹⁻³ Also, Gravenstein and Perkins noted the in-

TABLE III The calculated ED50 and ED95 doses of atropine at 5 and 10 min following administration of atropine-neostigmine mixture in groups A and B

	Neostigmine (Group A) $0.04 \text{ mg} \cdot \text{kg}^{-1}$		Neostigmine (Group B) $0.06 \text{ mg} \cdot \text{kg}^{-1}$	
	5 min	10 min	5 min	10 min
ED50 of atropine ($\text{mg} \cdot \text{kg}^{-1}$)	0.031	0.037	0.033	0.037
ED95 of atropine ($\text{mg} \cdot \text{kg}^{-1}$)	0.05	0.06	0.046	0.055

effectiveness of 0.6 to 1.5 mg atropine in abolishing the bradycardic effect of 0.2 to 0.83 mg neostigmine in volunteers.⁴ They concluded that about twice the weight of atropine was required to prevent neostigmine from lowering heart rates below base line.⁴ Fogdall and Miller⁹ examined equipotent doses of neostigmine and pyridostigmine (2.5 and $14.5 \text{ mg} \cdot 70 \text{ kg}^{-1}$ respectively) and found that atropine $1.0 \text{ mg} \cdot 70 \text{ kg}^{-1}$ (i.e., $0.014 \text{ mg} \cdot \text{kg}^{-1}$) was required to prevent bradycardia. In the present study, a significant reduction in heart rate was noted following the administration of a similar dose of neostigmine ($0.04 \text{ mg} \cdot \text{kg}^{-1}$) with higher doses of atropine up to $0.02 \text{ mg} \cdot \text{kg}^{-1}$ (Table I).

From this conflicting evidence, a question arises: what is the effective dose of atropine? At least, part of the great variability to atropine is because of inadequate dosing. Thus, we examined our data with logit analysis to predict the ED50 and ED95 doses of atropine when administered with neostigmine.

We found that the dose-response curves for atropine

TABLE IV Type and frequency of dysrhythmias

Drug combination	Frequency	Type
Group A		
0.04 mg/kg neostigmine + 0.014 mg/kg atropine	3/5 (60%)	A-V dissociation Premature ventricular contractions
0.0155 mg/kg atropine	3/5 (60%)	A-V dissociation
0.017 mg/kg atropine	1/5 (20%)	A-V dissociation
0.0215 mg/kg atropine	1/5 (20%)	First degree heart block
0.03 mg/kg atropine	1/5 (20%)	A-V dissociation
Group B		
0.06 mg/kg neostigmine + 0.0215 mg/kg atropine	3/5 (60%)	A-V dissociation
0.025 mg/kg atropine	1/5 (20%)	Bradycardia (heart rate < 50 beats/min)
0.035 mg/kg atropine	1/5 (20%)	Premature ventricular contractions
0.04 mg/kg atropine	1/5 (20%)	Bradycardia

(Figure) were parallel for both doses of neostigmine employed in this study (0.04 and $0.06 \text{ mg} \cdot \text{kg}^{-1}$) and the regression lines did not differ in position ($P = 0.79$). This indicates that the potency of atropine was similar in both groups. In fact, the estimated effective median dose (ED50) of atropine was similar in both groups (Table III), despite the higher dose of neostigmine ($0.06 \text{ mg} \cdot \text{kg}^{-1}$) given to patients in group B. The calculated ED95 doses of atropine were also similar in both groups. These results suggested that neostigmine had a ceiling effect with respect to its muscarinic activity on the heart.

In all but one group (B-1), a significant increase in heart rate was observed following administration of atropine. The maximum increase was observed at 1 min, and the maximum decreases were observed at 9–10 min (Tables I and II). Atropine has a short distribution half-life of about 1 min followed by a rapid decline of concentration within the first 8–10 min.¹⁰ Berghem *et al.* found that the amount of atropine remaining in the circulation at 10 min after IV injection corresponded to less than one per cent of the administered dose.¹¹ Hinderling *et al.*¹² found a relationship between heart rate and the logarithm of the calculated amounts of atropine in the peripheral compartment. Interestingly, we found a similar relationship between the logarithm of atropine dose administered and changes in heart rate (expressed as percentage from the control value), not only in this study but also in a similar study with edrophonium.¹³

The results of this study, when compared with our previously reported results with edrophonium,¹³ demonstrate that, at a higher dose range, equipotent doses¹⁴ of neostigmine ($0.06 \text{ mg} \cdot \text{kg}^{-1}$) or edrophonium ($1.0 \text{ mg} \cdot \text{kg}^{-1}$) required equal amounts of atropine to prevent bradycardia associated with their administration. The calculated ED50 doses of atropine at 5 and 10 min following administration of atropine and edrophonium ($1 \text{ mg} \cdot \text{kg}^{-1}$) mixture were 0.029 and $0.032 \text{ mg} \cdot \text{kg}^{-1}$ and ED95 doses were 0.055 and $0.05 \text{ mg} \cdot \text{kg}^{-1}$ respectively.¹³ Nevertheless, in a dose equipotent to neostigmine $0.04 \text{ mg} \cdot \text{kg}^{-1}$, edrophonium ($0.67 \text{ mg} \cdot \text{kg}^{-1}$) required half the amount of atropine to prevent bradycardia.¹³ The estimated ED50 doses of atropine at 5 and 10 min following administration of atropine and edrophonium ($0.67 \text{ mg} \cdot \text{kg}^{-1}$) mixture were 0.018 and $0.016 \text{ mg} \cdot \text{kg}^{-1}$ and ED95 doses were $0.024 \text{ mg} \cdot \text{kg}^{-1}$ respectively.¹³

Dysrhythmias, including A-V dissociation, premature ventricular contractions, first degree heart block and bradycardia have been reported following combinations of neostigmine and atropine.^{1–3} We observed similar dysrhythmias in both groups (Table IV). Samra *et al.* reported that the administration of neostigmine is associated with more profound bradycardia when given during halothane anaesthesia than during enflurane anaesthesia.¹⁵

Halothane is known to have negative chronotropic effects and to prolong A-V nodal conduction.¹⁶

In the present study, the effects of different combinations of atropine and neostigmine have been examined. The dose-response curves for atropine (following administration of the antagonistic mixture) were parallel for both doses of neostigmine employed in this study (0.04 and $0.06 \text{ mg} \cdot \text{kg}^{-1}$). The doses of atropine required to prevent neostigmine from decreasing heart rates below base line in 50 per cent (ED50) and 95 per cent of patients (ED95) were similar in patients who received neostigmine in doses of either $0.04 \text{ mg} \cdot \text{kg}^{-1}$ or $0.06 \text{ mg} \cdot \text{kg}^{-1}$. Under the conditions employed in this study, it would seem that in order to prevent late reductions in heart rates, the appropriate doses of atropine when used with neostigmine should be greater than that commonly used.

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References

- 1 Gottlieb JD, Sweet RB. The antagonism of curare: the cardiac effects of atropine and neostigmine. *Can Anaesth Soc J* 1963; 10: 114–21.
- 2 Baraka A. Safe reversal (2) – atropine-neostigmine mixture. An electrocardiographic study. *Br J Anaesth* 1968; 40: 30–6.
- 3 Rosner V, Kepes ER, Foldes FF. The effects of atropine and neostigmine on heart rate and rhythm. Recommendation for their use to reverse residual neuromuscular block. *Br J Anaesth* 1971; 43: 1066–74.
- 4 Gravenstein JS, Perkins HM. The effect of neostigmine, atropine and ephedrine on heart rate in man. *Anesthesiology* 1966; 27: 298–303.
- 5 Hocking RR. Criteria for selection of a subset regression: which one should be used? *Technometrics* 1972; 14: 967–70.
- 6 Armitage P. Statistical methods in medical research. First edition. London: Blackwell Scientific Publications, 1971; 269–301.
- 7 Jenrich RI, Moore RH. Maximum likelihood estimation by means of nonlinear least squares. In: Proceedings of the Statistical Computing Section. *Am Statist Assoc* 1975; 57–65.
- 8 Statistical Consultants, Inc. PCNONLIN and NONLIN84: Software for the statistical analysis of nonlinear models. The American Statistician 1986; 40: 52.
- 9 Fogdall RP, Miller RD. Antagonism of d-tubocurarine and pancuronium-induced neuromuscular blockades by pyridostigmine in man. *Anesthesiology* 1973; 39: 504–9.

- 10 Kanto J, Koltz U. Pharmacokinetic implications for the clinical use of atropine, scopolamine and glycopyrrolate. *Acta Anaesthesiol Scand* 1988; 32: 69–78.
- 11 Bergham L, Bergman U, Schildt B, Sorba B. Plasma atropine concentration determined by radioimmunoassay after single dose i.v. and i.m. administration. *Br J Anaesth* 1980; 52: 597–601.
- 12 Hinderling PH, Gundert-Remy U, Schmidlin O, Heinzel G. Integrated pharmacokinetics and pharmacodynamics of atropine in healthy humans. II: Pharmacodynamics. *J Pharm Sci* 1985; 75: 711–7.
- 13 Naguib M, Gomaa M, Absood GH. Atropine-edrophonium mixture: a dose-response study. *Anesth Analg* 1988; 67: 650–5.
- 14 Breen PJ, Doherty WG, Donati F, Bevan DR. The protencies of edrophonium and neostigmine as antagonists of pancuronium. *Anaesthesia* 1985; 40: 844–7.
- 15 Samra SK, Pandit UA, Pandit SK, Kothary SP. Modification by halogenated anaesthetics of chronotropic response during reversal of neuromuscular blockade. *Can Anaesth Soc J* 1983; 30: 48–52.
- 16 Atlee JL, Alexandra SC. Halothane effects on conductivity of the AV node and His-Purkinje system in the dog. *Anesth Analg* 1977; 56: 378–86.

Résumé

Nous avons voulu établir quelles doses d'atropine pouvaient prévenir le ralentissement du pouls chez 50 pour cent (DE50) et 95 pour cent (DE95) de nos 70 patients lors de l'usage de néostigmine après un bloc neuro-musculaire au pancuronium et aussi en bâtir les courbes dose-réponse. Nous avons mélangé $0.04 \text{ mg} \cdot \text{kg}^{-1}$ (groupe A, $n = 35$) ou $0.06 \text{ mg} \cdot \text{kg}^{-1}$ (groupe B, $n = 35$) de néostigmine avec au hasard, une de sept doses d'atropine s'échelonnant de 0.014 à $0.04 \text{ mg} \cdot \text{kg}^{-1}$ pour le groupe A et de 0.02 à $0.04 \text{ mg} \cdot \text{kg}^{-1}$ pour le groupe B. Les courbes dose-réponse de l'atropine sont construites à partir des mesures à cinq et dix minutes post-injection. Nous avons trouvé pour l'atropine, des courbes dose-réponse et des valeurs de DE50 et de DE95 semblables pour les deux groupes soit respectivement pour les groupes A et B, exprimées en $\text{mg} \cdot \text{kg}^{-1}$: DE50 à cinq minutes – 0.031 vs 0.033 ; à dix minutes – 0.037 vs 0.037 ; DE95 à cinq minutes – 0.05 vs 0.046 ; à dix minutes – 0.06 vs 0.055 . Il semble donc, d'après nos résultats, que les doses d'atropine nécessaires pour prévenir les bradycardies tardives avec la néostigmine soient plus grandes que celles employées habituellement.