Antagonism of d-tubocurarine-induced neuromuscular blockade with a mixture of 4-aminopyridine and neostigmine in man

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The antagonistic properties of a mixture of 4-aminopyridine (4-AP) 3 mg·ml⁻¹ and neostigmine 0.2 mg·ml⁻¹ (in three patient groups) administered at 90 per cent d-tubocurarine block were compared with those of plain neostigmine (in three patient groups) in thirty-six patients during thiopentone-fentanyl-nitrous oxide-oxygen anaesthesia. The recovery variables included thumb twitch height, thenar e.m.g. peak-to-peak amplitude, and train-of-four ratio in response to supramaximal ulnar nerve stimulation. In addition, mean arterial pressure, heart rate, apnoea time and time to responsiveness to verbal command after nitrous oxide was turned off at 20 minutes of recovery were examined as circulatory and central nervous system responses to antagonism. The addition of 4-AP 30 mg to neostigmine 2 mg enhanced the recovery of train-of-four ratio from 54.2 ± 5.2 to 80.2 ± 5.2 per cent at 20 mins of antagonism (mean ± SEM; $p < 0.01$) while adding 4-AP 45 mg to neostigmine 3 mg increased the train-of-four ratio from 67.7 ± 2.3 to 92.3 ± 2.4 per cent ($p < 0.01$) when compared with plain neostigmine. No statistically significant difference could be found between the groups in the recovery of twitch height or e.m.g. amplitude. The antagonism of d-tubocurarine block with 4-AP 30 mg plus neostigmine 2 mg was at least as effective as with neostigmine 3–4 mg. Mean arterial pressure increased in the group receiving 45 mg 4-AP

plus 3 mg neostigmine. Apnoea time and responsiveness to verbal command after discontinuation of controlled ventilation and nitrous oxide, respectively, were shortest in groups that received 30–45 mg 4-AP. The major adverse effect observed was temporary postoperative confusion in three of six patients who received 45 mg 4-AP. It is suggested that the use of 4-AP in combination with neostigmine should be restricted to cases where antagonism is not adequate with neostigmine and that the dose should not exceed 30 mg.

Key words

ANTAGONISTS, NEUROMUSCULAR RELAXANTS: neostigmine, 4-aminopyridine.

Four-aminopyridine (4-AP) facilitates neuromuscular transmission^{1,2} and also acts on other cholinergic synapses of the body.^{3,4} It is a rather weak antagonist of myoneural blockade itself, but has been shown to potentiate antagonism caused by anticholinesterases.^{5,6} Moreover, the combination of 4-AP and neostigmine might allow the use of smaller amounts of each drug, and might thus cause fewer side effects. The augmentory effect and long action of 4-AP⁷ could therefore be beneficial in situations where incomplete reversal with anticholinesterases alone at conventional dosages is a problem, e.g., in connection with relative muscle relaxant overdosage and with other impairing derangements of neuromuscular transmission. On the other hand, the benefits of 4-AP may be counteracted by its unspecific action on other synapses.

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With this background in mind, we wished to clarify whether a fixed-dose mixture of 4-AP and neostigmine could offer advantages over plain neostigmine with respect to recovery from d-tubocurarine blockade and incidence and severity of side effects.

Methods

Patients

Thirty-six patients (ASA physical status class I-II) who gave their informed consent were openly matched in six comparable groups according to sex, type of surgery, age and weight (Table I). There were no diseases or medications that could affect neuromuscular function in the recent preoperative history of the patients. The possibility of pregnancy in the female patients was ruled out by inquiry. The study plan was approved by the ethics committee of the institute.

Anaesthetic technique

Premedication was with oxycodone $0.14 \text{ mg} \cdot \text{kg}^{-1}$, promethazine 25 or 50 mg and atropine $0.01 \text{ mg} \cdot \text{kg}^{-1}$ i.m. 60–90 minutes prior to anaesthesia. All patients received a balanced anaesthetic (thiopentone-fentanyl-70 per cent nitrous oxide in oxygen). Succinylcholine $1 \text{ mg} \cdot \text{kg}^{-1}$ was used to facilitate tracheal intubation. After recovery from the depolarizing block, a 90 per cent competitive blockade was induced with an initial dose of d-tubocurarine $0.3 \text{ mg} \cdot \text{kg}^{-1}$ plus additional boluses if needed, and was maintained at 90–95 per cent with small increments until reversal at 90 per cent block. Ventilation was adjusted to keep end-tidal CO_2 between 5.0–5.5 per cent (Datex CD 300®, Instrumentarium, Helsinki).

Monitoring and antagonism of neuromuscular block

The left ulnar nerve was stimulated with supramaximal bipolar square wave pulses through steel needle electrodes at the wrist, with 0.1 ms of duration and at a frequency of 0.1 Hz. The evoked thumb adduction twitch height and thenar electromyographic peak-to-peak amplitude measured with 27 gauge needles in the adductor pollicis muscle (Transient Recorder DL 905®, Datalab) were recorded on a dual-channel paper recorder. During recovery from neuromuscular block, a train-of-four stimulus was delivered at 0, 5, 10 and 20 mins after antagonist injection. In the six groups, the follow-

ing doses of antagonists were given to reverse the 90 ± 2 per cent block:

- Group 1: neostigmine 2 mg + atropine 1 mg
- Group 2: neostigmine 3 mg + atropine 1.5 mg
- Group 3: neostigmine 4 mg + atropine 2 mg
- Group 4: 4-AP* 15 mg + neostigmine 1 mg + atropine 0.5 mg
- Group 5: 4-AP 30 mg + neostigmine 2 mg + atropine 1 mg
- Group 6: 4-AP 45 mg + neostigmine 3 mg + atropine 1.5 mg

The administration of nitrous oxide was continued and ventilation was controlled during the recovery measurements. If the patient started to react to the tracheal tube, increments of 25 to 50 mg thiopentone were given. Heart rate was noted and blood pressure measured with a sphygmomanometer at 1 minute intervals up to 10 mins, and thereafter at 2 minutes. At 20 mins after the antagonist injection, nitrous oxide was turned off and apnoea time and patient response to auditory stimuli were noted. The patients were under observation in the recovery room for at least two hours, and an interview was made on the first postoperative day by one of the authors (KW).

The statistical analysis of the data was performed by using one-way analysis of variance, the Bonferroni t test for multiple comparison of groups and Fisher's fourfold test. The difference was considered as statistically significant at a level of $p < 0.05$.

Results

There was no statistically significant difference between the groups in the duration of 90 per cent neuromuscular blockade or the total dose of d-tubocurarine (Table I). The dose of fentanyl given for supplementation was not significantly different between the groups (Table I).

Recovery of neuromuscular transmission

The results of neuromuscular recovery are shown in Table II. Increasing the plain neostigmine dosage from 2 mg to 3 and 4 mg did not modify the recovery of twitch or emg amplitude. Increasing the dose of neostigmine from 2 to 3 mg had no significant effect on the restitution of the train-of-four ratio. Increas-

*Pymadin®; Pharmacim, Bulgaria.

TABLE I Basic data for the patient groups

	Neostigmine + 4-AP (mg)	Sex (M/F)	Age (yrs)	Weight (kg)	Type of operation (surface/ abdominal)	Duration of 90% block (min)	Total d-tubo- curarine dose (mg)	Dose of fentanyl for supplementa- tion ($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$)
Group 1	2 + 0	3/3	43.2 $\pm$ 6.1	70.3 $\pm$ 6.0	5/1	24.5 $\pm$ 7.0	27.3 $\pm$ 2.5	3.52 $\pm$ 0.4
Group 2	3 + 0	3/3	41.3 $\pm$ 3.5	69.2 $\pm$ 2.6	6/0	52.7 $\pm$ 12.3	29.0 $\pm$ 3.7	3.62 $\pm$ 0.3
Group 3	4 + 0	3/3	41.4 $\pm$ 5.6	78.0 $\pm$ 5.9	5/1	42.2 $\pm$ 7.6	31.1 $\pm$ 2.9	2.40 $\pm$ 0.1
Group 4	1 + 15	3/3	40.0 $\pm$ 5.8	74.3 $\pm$ 4.1	5/1	42.7 $\pm$ 6.1	29.5 $\pm$ 1.8	3.38 $\pm$ 0.4
Group 5	2 + 30	3/3	45.4 $\pm$ 6.8	61.5 $\pm$ 2.6	4/2	35.2 $\pm$ 6.6	25.0 $\pm$ 1.9	3.33 $\pm$ 0.3
Group 6	3 + 45	3/3	43.3 $\pm$ 7.1	68.4 $\pm$ 4.4	5/1	59.3 $\pm$ 11.8	31.0 $\pm$ 2.0	3.58 $\pm$ 0.3

Number of cases or mean $\pm$ SEM.

ing the neostigmine dose from 3 mg to 4 mg did not produce more recovery of the mechanical twitch or of the e.m.g. train-of-four ratio.

Antagonism with the combination of 4-AP 15 mg and neostigmine 1 mg was comparable to neostigmine 2 mg. One patient in both of these groups needed an additional dose of neostigmine (1 mg) due to the poor train-of-four ratio recovery (31 and 33 per cent at 20 min).

There was no statistically significant difference in the early phase of twitch recovery or the recovery of e.m.g. amplitude between the group receiving 4-AP 30 mg plus neostigmine 2 mg and the group which received plain neostigmine 2 mg. Four-AP 30 mg plus neostigmine 2 mg and 4-AP 45 mg plus neostigmine 3 mg, respectively, significantly improved antagonism of the train-of-four ratio, compared with plain neostigmine (Table II). The mix-

TABLE II Recovery of neuromuscular variables

Antagonism	Twitch tension (%)			EMG amplitude (%)		
	5 min	10 min	20 min	5 min	10 min	20 min
Neostigmine 2 mg	60.3 $\pm$ 9.4	91.5 $\pm$ 9.8	108.8 $\pm$ 8.1	56.7 $\pm$ 8.4	79.2 $\pm$ 7.7	93.2 $\pm$ 6.1
Neostigmine 3 mg	70.2 $\pm$ 8.5	89.7 $\pm$ 7.4	95.7 $\pm$ 6.5	76.3 $\pm$ 5.3	90.7 $\pm$ 6.2	97.2 $\pm$ 5.7
Neostigmine 4 mg	76.2 $\pm$ 7.4	94.7 $\pm$ 7.5	100.8 $\pm$ 7.4	72.3 $\pm$ 8.6	92.0 $\pm$ 7.3	97.3 $\pm$ 6.2
Neostigmine 1 mg + 4-AP 15 mg	57.5 $\pm$ 5.6	80.5 $\pm$ 8.4	96.7 $\pm$ 9.0	63.8 $\pm$ 8.0	81.2 $\pm$ 7.5	94.7 $\pm$ 6.4
Neostigmine 2 mg + 4-AP 30 mg	89.7 $\pm$ 7.8	114.0 $\pm$ 8.8	119.2 $\pm$ 8.0	91.8 $\pm$ 8.3	105.0 $\pm$ 7.5	108.5 $\pm$ 6.9
Neostigmine 3 mg + 4-AP 45 mg	87.5 $\pm$ 7.1	102.0 $\pm$ 5.7	107.0 $\pm$ 4.1	83.0 $\pm$ 4.5	94.0 $\pm$ 5.1	97.7 $\pm$ 5.6
Antagonism	Train-of-four (%)			EMG train-of-four (%)		
	5 min	10 min	20 min	5 min	10 min	20 min
Neostigmine 2 mg	23.8 $\pm$ 3.7	38.5 $\pm$ 5.5	54.2 $\pm$ 5.2	24.2 $\pm$ 3.3	39.0 $\pm$ 5.4	59.7 $\pm$ 6.0
Neostigmine 3 mg	36.7 $\pm$ 5.0	55.3 $\pm$ 3.3	67.7 $\pm$ 2.3	43.3 $\pm$ 3.9	63.0 $\pm$ 4.3	75.8 $\pm$ 3.6
Neostigmine 4 mg	39.2 $\pm$ 1.9	51.0 $\pm$ 2.1	62.5 $\pm$ 1.7	34.7 $\pm$ 6.9	52.6 $\pm$ 8.2	63.8 $\pm$ 7.0
Neostigmine 1 mg + 4-AP 15 mg	21.5 $\pm$ 3.6	36.7 $\pm$ 5.1	54.7 $\pm$ 6.2	21.5 $\pm$ 4.0	37.7 $\pm$ 5.9	59.2 $\pm$ 8.5
Neostigmine 2 mg + 4-AP 30 mg	43.8 $\pm$ 7.4	65.2 $\pm$ 8.2*	80.2 $\pm$ 5.2†	49.2 $\pm$ 6.8	74.3 $\pm$ 8.1	86.2 $\pm$ 6.0
Neostigmine 3 mg + 4-AP 45 mg	68.7 $\pm$ 5.8†	87.2 $\pm$ 3.6†	92.3 $\pm$ 2.4†	66.0 $\pm$ 8.7	87.7 $\pm$ 3.9*	97.2 $\pm$ 2.2*

Time after antagonist administration. * $p < 0.05$, † $p < 0.01$; group 5 vs. group 1, group 6 vs. group 2; the Bonferroni t-test for multiple comparison of groups.

FIGURE Circulatory response to antagonism of myoneural blockade. HR = heart rate, MAP = mean arterial pressure. ** $p < 0.01$; group 6 vs. group 2; the Bonferroni *t* test. Time after antagonist administration at ten per cent twitch height.

ture of 30 mg 4-AP and 2 mg neostigmine produced faster train-of-four recovery than that obtained with 3 or 4 mg plain neostigmine (Table II). The difference was, however, not statistically significant.

At 20 min after the administration of the antagonist mixture there were significantly more patients in groups 5 and 6 who had a train-of-four ratio of over 70 per cent than there were among their counterparts who received plain neostigmine, i.e., groups 1 and 2 (Table III).

Side-effects

Circulatory response

In all patient groups heart rate response to antagonism showed initial tachycardia and later slowing of the heart rate. When the groups receiving equal amounts of atropine (group 1 vs. group 5, group 2 vs. group 6) were compared, 4-AP was not seen to modify this response (Fig. 3). However, the patients receiving the highest 4-AP dose displayed a larger increase in the mean arterial pressure (MAP)

than did the other groups (Fig. 1). The difference was significant at three minutes of recovery between groups 2 and 6 (-0.6 ± 2.1 mmHg and 19.4 ± 6.1 mmHg, respectively, $p < 0.01$). Increments of thiopentone 25–50 mg were needed in ten patients, up to a total dose of 175 mg in one patient in group 6, for supplementation of sleep during antagonism. This added thiopentone had no effect on heart rate or pressure trends. There were four episodes of junctional arrhythmia: one patient in group 1 and in group 3, two patients in group 6. We saw no evidence of ventricular ectopic rhythm.

Recovery from anaesthesia

When patients receiving 4-AP and neostigmine (group 5 + group 6) were compared with those receiving plain neostigmine (group 1 + group 2), the apnoea time (1.4 ± 0.4 min) was shorter in the 4-AP groups than in the plain neostigmine groups (4.8 ± 1.0 min; mean $\pm$ SEM, $p < 0.005$). After discontinuation of nitrous oxide, patients receiving 4-AP responded to verbal command in 3.6 ± 1.0 min. This was sooner than the 6.5 ± 0.7 min recorded in the patients who received plain neostigmine ($p < 0.05$).

The recovery room period

Antagonism of the neuromuscular blockade was adequate in all patients, according to clinical criteria. Postoperative shivering was observed in nine patients, evenly distributed among the groups. Three cases of confusion, expressed as difficulty in orientation in time and place were seen in the immediate postoperative period. All these patients had received 45 mg of 4-AP (range 0.59 – 0.76 mg·kg⁻¹). The confusion lasted from 10 to 60 min and was associated in one patient with restlessness. No such episodes were detected in any other patient group. During the postoperative inquiry, the general recovery from anaesthesia was rated as unpleasant by 35 per cent of the 4-AP patients and by six per cent of the patients who received plain neostigmine. The difference was not statistically significant ($p = 0.12$).

Discussion

The results show that 4-aminopyridine enhanced the reversal effect of neostigmine when the latter was used in recommended clinical doses to antagonize a 90 per cent d-tubocurarine block during balanced anaesthesia. This was clearly evident as a faster

TABLE III Train-of-four ratios

	TOF-ratio at 20 min <70% / >70%
Group 1	6/0
Group 2	4/2
Group 3	6/0
Group 4	5/1
Group 5	1/5*
Group 6	0/6†

Frequency distribution of patients with train-of-four ratio under 70 per cent and over 70 per cent at 20 min after administration of the antagonist mixtures.

*Gr. 5 vs. Gr. 1: $p = 0.025$;

†Gr. 6 vs. Gr. 2: $p = 0.05$; Fisher's exact fourfold test.

restitution of the train-of-four ratio but less so in the recovery of twitch height or peak-to-peak amplitude of the e.m.g. Clinically we were unable to detect any significant benefit of 4-AP usage as regards recovery from neuromuscular block. However, the number of patients in this study was small, and much more time was allowed for antagonism than is feasible in clinical practice.

The observed facilitatory effect of 4-AP on neostigmine reversal of neuromuscular blockade is in accordance with results obtained in animals^{6,8} as well as in man.⁵ Miller *et al.*⁵ reported that only one-third of the usual neostigmine dose was needed when combined with 0.35 mg·kg⁻¹ 4-AP to achieve the same 50 per cent antagonistic effect during pancuronium block in man. In our study 15 mg of 4-AP (0.20 mg·kg⁻¹) combined with 1 mg of neostigmine (13.5 mg·kg⁻¹) produced antagonism equal to 2 mg plain neostigmine (28 µg·kg⁻¹), while 4-AP 30 mg (0.49 mg·kg⁻¹) combined with neostigmine 2 mg (28 µg·kg⁻¹) was at least as effective as 4 mg plain neostigmine (51 µg·kg⁻¹). This indicates an interaction of the same degree between 4-AP and neostigmine in the antagonism of pancuronium or d-tubocurarine block in terms of twitch height recovery. Miller *et al.*⁵ did not use train-of-four ratio or other fading responses as an index of recovery of neuromuscular block, and the possible differences between the effects of 4-AP on the recovery from pancuronium and d-tubocurarine blocks cannot consequently be discussed here.

A train-of-four ratio greater than 70 per cent is claimed to correlate well with clinical tests of adequacy of respiration.⁹ Only 2 of 12 patients in

this study, receiving 2 to 3 mg neostigmine, reached this critical margin, although we could not detect clinically significant muscle weakness in any of the patients. In contrast, in 11 of 12 patients the train-of-four ratio recovered up to 70 per cent or more with the addition of 4-AP.

In addition to postjunctional receptor blockade, d-tubocurarine is postulated to act on prejunctional membrane receptors which are thought to enhance acetylcholine mobilization from reserve to readily releasable stores.¹⁰ According to a hypothesis put forward by Bowman,¹¹ neuromuscular block by prejunctional mechanism is characterized by fading responses after repetitive nerve stimulation at 2 Hz. The augmentatory effect of 4-AP in combination with neostigmine on restoration of train-of-four fade suggests that when the breakdown of released acetylcholine is hindered by neostigmine, 4-AP may also support the mechanisms of mobilization of acetylcholine restricted by prejunctional d-tubocurarine block.

Four-AP readily penetrates the blood brain barrier. It has been shown to enhance the recovery from ketamine-diazepam anaesthesia,^{12,13} and convulsions have been seen in patients with doses exceeding 1 mg·kg⁻¹.¹⁴ The mean awakening time of our patients not receiving 4-AP was of the order found by Heinonen *et al.* who used essentially the same anaesthesia regimen.¹⁵ The shorter awakening time in our patients after 4-AP demonstrates that 4-AP antagonized nitrous oxide-oxygen sleep after balanced anaesthesia supplemented with opiates and relaxants. From a study conducted on humans, Sia and Zandstra claim that 4-AP antagonizes respiratory depression after fentanyl.¹⁶ The shortening of apnoea time in our patients is in accordance with those results.

Only the largest dose of 4-AP modified the circulatory response to antagonism in our patients. Arterial pressure was also increased while heart rate remained stable when 4-AP was administered to dogs under balanced anaesthesia¹⁷ and to dogs and cats under chloralose anaesthesia,¹⁸ while 4-AP was shown to reverse polymyxin b-induced hypotension but not bradycardia in anaesthetized cats.¹⁹ Although the observed pressure response to 4-AP might appear clinically benign in connection with the postulated inotropic effects of 4-AP on cardiac muscle, considerable increases in external cardiac work can result. This has been shown to occur in

anaesthetized dogs.^{17,18} These cardiovascular effects as well as abrupt reversal of anaesthesia after 4-AP could prove deleterious for a patient with limited coronary vascular reserve.

To conclude, in man a fixed dose mixture of 4-AP and neostigmine containing 30 mg of 4-AP to 2 mg neostigmine clearly potentiates the reversal of d-tubocurarine induced train-of-four fade as a possible sign of prejunctional antagonism, compared with plain neostigmine in corresponding conventional doses. The mixture, however, caused adverse effects in amounts containing 45 mg of 4-aminopyridine. Thus, owing to the narrow therapeutic width of 4-AP, a fixed dose mixture for reversal as a routine method seems unwarranted. The use of 4-AP should be kept in reserve for cases not responding sufficiently to anticholinesterase therapy. In these cases the dose of 4-aminopyridine should not exceed 30 mg.

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Résumé

Chez 36 malades maintenus sous anesthésie au thiopentone-fentanyl-protoxyde d'azote et d-tubocurarine, on a comparé les propriétés de renversement du block neuromusculaire d'un mélange de 4-aminopyridine (4-AP) 3 mg·ml⁻¹ et de néostigmine 0.2 mg·ml⁻¹ à la néostigmine employée seule. Les variables, traduisant la récupération, qu'on a mesurées étaient les suivantes: amplitude de la réponse du pouce au twitch, électromyogramme de l'éminence thénar, amplitude d'un pic à l'autre et rapport du train de quatre en réponse à une stimulation supra-maximale du nerf cubital. Vingt minutes après l'administration des drogues, on a enregistré les pressions artérielles moyennes et les fréquences cardiaques lesquelles traduisaient la réponse circulatoire au mélange; comme indice de la réponse du système nerveux central à ces drogues, on a mesuré la durée de l'apnée et le délai à réagir à des incitations verbales après le retrait du protoxyde d'azote.

Comparée à la néostigmine pure, l'addition de 4-AP 30 mg à 2 mg de néostigmine a accéléré la récupération du rapport train de quatre de 54.2 ± 5.2% à 80.2 ± 5.2% (moyenne ± SEM; $p < 0.01$); l'addition de 4-AP 45 mg à 3 mg de néostigmine a elle aussi accéléré cette récupération de 67.7 ± 2.3% à 92.3 ± 2.4% ($p < 0.01$).

Pour l'amplitude au twitch et l'électromyogramme de l'éminence thénar, les différences observées n'ont pas atteint les niveaux de significativité statistique. Le renversement du bloc à la d-tubo avec le mélange 4-AP 30 mg plus néostigmine 2 mg est comparable à celui obtenu avec néostigmine 3-4 mg. On a observé une augmentation de la pression artérielle moyenne dans le groupe qui a reçu 4-AP 45 mg plus 3 mg de néostigmine. Le temps d'apnée et le délai de réponse aux incitations verbales ont été les plus courts chez les patients recevant 30 et 45 mg de 4-AP. L'effet indésirable notable qu'on a observé a été l'apparition d'une confusion post-opératoire transitoire dans trois des six patients qui ont reçu 45 mg de 4-AP. Nous suggérons que l'adjonction de 4-AP à la néostigmine ne devrait s'employer que pour ces cas où le renversement est insuffisant avec la néostigmine et alors la dose ne devrait pas dépasser les 30 mg.