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Postoperative Residual Paralysis and Respiratory Status: A Comparative Study of Pancuronium and Vecuronium

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Summary

The objective of this prospective double-blind study was to determine whether postoperative residual paralysis (PORP) after pancuronium or vecuronium results in hypoxemia and hypercapnia in the immediate admission period to the recovery ward. Eighty-three consecutive surgical patients received balanced or intravenous anesthesia with pancuronium for operations lasting longer than one hour or vecuronium for those lasting less than 60 min, both combined with neostigmine at the end of anesthesia. Standard clinical criteria assessed neuromuscular function intraoperatively. Postoperatively, we determined neuromuscular function (acceleromyography with supramaximal train-of-four (TOF) stimulation of the ulnar nerve, and a 5-s head lift) and pulmonary function (pulse oximetry: SpO_2, and blood gas analysis: SaO_2, $PaCO_2$). We defined PORP as a TOF-ratio <70 %, hypoxemia as a postoperative SpO_2 ≥5 % below the pre-anesthestic level together with a postoperative SaO_2 <93 %, and hypercapnia as a $PaCO_2$ ≥46 mm Hg. Among the 49 pancuronium and 27 vecuronium patients studied, the PORP rates were 20 % in the pancuronium group and 7 % in the vecuronium group ($p>0.05$). Hypoxemia and hypercapnia occurred more often in pancuronium patients with PORP than in those without PORP namely 60 % vs. 10% ($p<0.05$) and 30 % vs. 8 % ($p>0.05$), respectively. We conclude that PORP after pancuronium is a significant risk factor for hypoxemia.

Key words

Postoperative residual paralysis •Pancuronium • Vecuronium • Neuromuscular function • Pulse oximetry • Arterial blood gas analysis • Pulmonary function • Hypoxemia • Hypercapnia

Introduction

The incidence of postoperative residual neuromuscular block occurs in 20-50 % of patients after the use of long-acting muscle relaxants such as pancuronium, d-tubocurarine or gallamine, but only in 0-13.6 % of patients after intermediate-acting agents such as vecuronium or atracurium (Viby-Mogensen *et al.* 1979, Andersen *et al.* 1988, Beemer and Rozental 1986, Bevan *et al.* 1988, Howardy-Hansen *et al.* 1989, Fawcett *et al.* 1995). Previous data have shown that patients with incomplete recovery of neuromuscular function tend to develop postoperative pulmonary complications. However, a significant relationship between postoperative residual paralysis (PORP) and postoperative impairment of pulmonary function, i.e.

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hypoxemia or hypercapnia, could not yet be proven conclusively (Pedersen *et al.* 1992, Pedersen 1994). This is possibly due to the fact that interrelated anesthesiological, surgical and patient-related factors can play a role (Duncan and Cohen 1987, Beemer and Rozental 1986, Miller 1989, Pedersen *et al.* 1990, 1992, Pedersen 1994). Furthermore, since PORP is rapidly self-limiting and can therefore only briefly interact with pulmonary function, it is difficult to show a cause-and-effect relationship between PORP and impaired pulmonary function.

The objective of the present prospective double-blind study was therefore to determine the incidence of postoperative hypoxemia and hypercapnia after the use of the long-acting pancuronium or the intermediately-acting vecuronium. Furthermore, we investigated whether a causal relationship exists between the impaired pulmonary function and PORP immediately after admission of patients to the recovery ward. Standard routine anesthesiological procedures and practices have been followed and employed.

Materials and Methods

Eighty-three consecutive patients, ASA physical status I-III, were considered for inclusion in the study after obtaining their written informed consent and approval of the University Ethics Committee. The patients had been scheduled for elective intraabdominal surgery requiring the use of non-depolarizing neuromuscular blocking agents. The patients were anesthetized by regular staff members of the department. The attending anesthesiologist was responsible for selection of the drugs used for premedication, anesthesia and neuromuscular blockade, and followed the standard guidelines, practices and procedures of our hospital. However, he was not informed that the patients were to be assessed in the recovery ward.

Premedication consisted of oral midazolam (7.5 mg). We administered methohexitone (1.5 mg kg^{-1} i.v.) for induction of anesthesia and succinylcholine (1.5 mg kg^{-1} i.v.) for intubation. Anesthesia was continued with N_2O:O_2 in a 2:1 ratio, either as balanced anesthesia (BA – enflurane or isoflurane together with fentanyl and a neuromuscular blocking agent) or as intravenous anesthesia (IVA – midazolam or propofol together with fentanyl and a neuromuscular blocking agent). We used pancuronium plus fentanyl or vecuronium plus fentanyl for operations with an expected duration longer or less than one hour, respectively. The applied muscle relaxant determined the inclusion of the patient in either the pancuronium or the vecuronium study group, each of which was further divided into two subgroups according to the patient's train-of-four (TOF) ratios (≥ 0 %, or <70 %). We adjusted the intraoperative relaxation as required according to standard clinical criteria. To prevent hypothermia (<36 °C), we used heating pads and warming blankets (also covering the arms and hands), and additional humidifiers as well as intravenous fluid warmers, when necessary.

Neostigmine (1.5 mg i.v.) and atropine (0.5 mg i.v.) were routinely administered at the end of the operation. The patients were extubated and taken to the recovery ward once residual curarization was no longer present according to usual clinical criteria. We kept a record of pre-existing pulmonary diseases, surgically and anesthesiologically relevant data, and the interval between injection of the reversal agent and testing in the recovery ward. As soon as the attending anesthesiologist had left the recovery ward, all patients capable of complying with instructions were assessed by an investigator, who was not involved in any way in the administration of anesthesia and was uninformed about the muscle relaxant used. Patients who were not sufficiently awake, oriented and cooperative were excluded from the study.

We performed relaxometric and clinical examinations to detect possible residual paralysis as well as simultaneous pulse oximetry and blood-gas analysis to determine the respiratory status. In addition, the temperature was measured rectally and superficially on the skin over the thenar musculature of the hand used for neuromuscular monitoring. The patients breathed room air during an approximately 10-min examination. The hand, wrist and forearm were immobilized in a splint and neuromuscular function was monitored with a nerve stimulator (Accelograph™, Biometer, Denmark) using supramaximal TOF stimulation of the ulnar nerve at the wrist (2 Hz over 2 s, repeated every 12 s). We used the mean of three consecutive TOF ratios (i.e. the ratios of the fourth to the first responses of the thumb to TOF stimulation) for the evaluation. TOF ratios ≥70 % were regarded as adequate neuromuscular recovery, TOF ratios <70 % as residual paralysis (PORP) (Brand *et al.* 1977). Clinically, the ability to sustain a head lift for at least 5 s was taken as the criterion of recovery. The test was recorded as "adequate head lift" if this was possible, or "weak head lift" if it was not. Signs of impaired breathing

such as a deficiency in coordination, the use of auxiliary respiratory muscles, or signs of airway obstruction were also noted.

We detected hypoxemia by pulse oximetry determining the peripheral hemoglobin oxygen saturation (SpO_2, MARS system, Hewlett-Packard Co.) and by simultaneous arterial blood gas analysis determining the arterial hemoglobin oxygen saturation (SaO_2). In addition, we detected hypercapnia by simultaneously measuring arterial CO_2 partial pressure ($PaCO_2$). The SpO_2 value was accepted as reliable, when patient-induced movement artifacts and dislocation of the pulse oximeter probe could be excluded, the signal quality was stable, and the saturation level remained constant for ≥2 min (Petry 1995, Georgiou *et al.* 1996). Hypoxemia was considered to be present if the postoperative SpO_2 level was ≥5 % below the baseline pre-anesthetic SpO_2 level, and if SaO_2 was <93 % at the same time. Hypercapnia was considered present if $PaCO_2$ was ≥46 mm Hg. This concluded the assessment, after which further care (e.g. oxygen, an additional dose of neostigmine if required, and analgesia) was tailored to each patient's needs.

The results are expressed as mean ± standard deviation (SD), range, absolute values and per cents. Statistical analysis was performed, applying analysis of variance or Student's unpaired t-test for interval scale quantitative data, logistic regression analysis for comparison of dichotomous quantitative data, and the chi-square test for comparison of frequencies. The value of $p<0.05$ was considered significant.

Table 1. Duration of anesthesia, number (%) of the type of anesthesia, dose of muscle relaxant, and the time interval between reversal and testing in the recovery room in the pancuronium and vecuronium groups and their subgroups (TOF ≥70 % or <70 %).

	Duration [min.]	Type of anesthesia BA	IVA	Dose [mg]	[μg kg^{-1} h^{-1}]	Interval [min]
Pancuronium (n = 49)	83.2±38.2* (21-218)	30 (61 %)	19 (39 %)	4.7±1.31 (3-8)	55±22.7 (22-159)	13.9±7.19 (5-35)
TOF ≥70 % (n=39)	80.4±38.5 (21-218)	25 (64 %)	14 (36 %)	4.6±1.28 (3-8)	56±24.0 (24-159)	14.3±6.97 (5-35)
TOF <70 % (n=10)	94.4±34.9 (45-150)	6 (60 %)	4 (40 %)	5.2±1.33 (3-8)	52±16.1 (22-80)	12.2±7.74 (5-29)
Vecuronium (n=27)	49.8±17.2 (20-75)	18 (67 %)	9 (33 %)	4.3±1.24 (2-7)	88±33.9 (43-192)	12.2±7.36 (5-30)
TOF ≥70 % (n=25)	49.6±16.6 (20-75)	17 (68 %)	8 (32 %)	4.2±1.27 (2-7)	86 ± 32.2 (43-192)	12.2±7.34 (5-30)
TOF < 70% (n=2)	28, 75	1 (50 %)	1 (50 %)	4.0, 5.2	67, 156	0, 15

Data are mean ± SD (range), TOF = train-of-four ratio [%], BA – balanced anesthesia, IVA – intravenous anesthesia.
** $p<0.05$: pancuronium vs. vecuronium*

Results

Altogether 76 patients were included in the study. Forty-nine patients received pancuronium and 27 patients received vecuronium. Four pancuronium and 3 vecuronium patients were excluded from the study because of poor cooperation or failure to be adequately awake during clinical testing. Because only a few vecuronium patients had a TOF ratio of <70 %, it was not possible to compare the vecuronium subgroups statistically. However, their data are still presented descriptively in the corresponding tables, where they were relevant for completeness of the study. Therefore, the pancuronium and vecuronium groups as well as the two pancuronium subgroups (TOF ratio ≥70 % or <70 %) were compared.

The pancuronium and the vecuronium study groups as well as the two pancuronium subgroups (TOF ratio ≥70 % or <70 %) did not differ significantly in regard to the age, weight and height. The duration of

anesthesia in the pancuronium group was longer than in the vecuronium group (Table 1, $p<0.05$). Pancuronium doses in the subgroups were identical, as was the interval between reversal and testing in the recovery ward, both between the general pancuronium and vecuronium study groups, and between the pancuronium subgroups. There were also no statistically significant differences in the frequencies of anesthesia types between the general pancuronium and the vecuronium study groups, or between the pancuronium subgroups (Table 1). The core temperatures of patients, on arrival in the recovery ward, ranged from 36.1 to 37.2 °C and their peripheral temperatures were between 32.5 to 35.2 °C.

Table 2. Train-of-four ratio (TOF) and number of patients demonstrating residual paralysis in the pancuronium and vecuronium groups according to relaxometric (TOF <70 %) and clinical criteria (weak head lift).

		TOF [%]	**Number of patients (%) TOF < 70%**	**Weak head lift**
Pancuronium	(n=49)	78±17.6* (37-100)	10 (20 %)	3 (6 %)
Vecuronium	(n=27)	92±11.0 (59-100)	2 (7 %)	1 (4 %)
Total	(n=76)	85±7.2	12 (16 %)	4 (5 %)

*Data are mean ± S.D. (range). * $p<0.05$: pancuronium vs. vecuronium*

The incidence of TOF ratios <70 % was three times higher in pancuronium patients than in those given vecuronium ($p>0.05$). Correspondingly, the mean TOF ratio in the pancuronium group was significantly lower than in the vecuronium group ($p<0.05$). All patients with a weak head-lift had a TOF ratio <70%. However, the head-lift test was observed in only 4 of the 12 patients with a TOF ratio <70 % (Table 2). No patient showed clinical signs of impaired breathing, such as deficiencies in coordination, the use of auxiliary respiratory muscles, or signs of airway obstruction.

Table 3. Number of postoperative patients (%) with hypoxemia or hypercapnia, and the total number of patients (Total) with pulmonary impairment (hypoxemia alone, hypercapnia alone or both together) in the pancuronium and vecuronium groups. The groups are separated into subgroups according to the magnitude of TOF (≥70 % or < 70%). TOF = train-of-four ratio [%].

Postoperative pulmonary impairment		**Hypoxemia**	**Hypercapnia**	**Total**
Pancuronium	(n=49)	10 (20 %)	6 (12 %)	12 (25 %)
TOF ≥70 %	(n=39)	4 (10 %)	3 (8 %)	5 (13 %)
TOF <70 %	(n=10)	6 (60 %)*	3 (30 %)	7 (70 %)*
Vecuronium	(n=27)	7 (26 %)	2 (7 %)	8 (30 %)
TOF ≥70 %	(n=25)	7 (28 %)	2 (8 %)	8 (32 %)
TOF <70 %	(n= 2)	0 (0 %)	0 (0 %)	0 (0 %)

*TOF – train-of-four ratio [%], * $p< 0.05$: pancuronium TOF <70 % vs. pancuronium TOF ≥70 %*

Table 4. Number of patients/total number of patients in the respective subgroups (in %) with postoperative pulmonary impairment (i.e. hypoxemia alone, hypercapnia alone, or both together, according to last column, "Total" in Table 4) in the pancuronium and vecuronium groups and their subgroups (TOF ≥70 % or < 70%), according to type of anesthesia.

Type of anesthesia	Postoperative pulmonary impairment BA	IVA
Pancuronium (n=49)	7/30 (23 %)	5/19 (26 %)
TOF ≥70 % (n=39)	3/25 (12 %)	2/14 (14 %)
TOF < 70 % (n=10)	4/6 (67 %)*	3/4 (75 %)*
Vecuronium (n=27)	5/18 (28 %)	3/9 (33 %)
TOF ≥70 % (n=25)	5/17 (29 %)	3/8 (38 %)
TOF <70 % (n= 2)	0/1 (0 %)	0/1 (0 %)

p<0.05: pancuronium TOF <70 % vs. pancuronium TOF ≥70 %, TOF – train-of-four ratio [%], BA – balanced anesthesia, IVA – intravenous anesthesia.

Table 5. Doses ($\mu g\ kg^{-1}h^{-1}$) of fentanyl in patients without or with postoperative pulmonary impairment (i.e. hypoxemia alone, hypercapnia alone, or both together, according to the last column, "Total" in Table 4) in the pancuronium and vecuronium groups and their subgroups (TOF ≥70 % or <70 %).

		Fentanyl dose without pulmonary impairment	Fentanyl dose with pulmonary impairment	Respiratory disease Total	Respiratory disease with pulmonary impairment
Pancuronium	(n=49)	5.0±1.3 (2.4- 8.5)	4.9±1.04 (3.5-7.6)	8 (16 %)	2 (25 %)
TOF ≥70 %	(n=39)	4.9±1.3 (2.4- 9.5)	4.7±0.58 (3.9-5.7)	6 (15 %)	2 (33 %)
TOF <70 %	(n=10)	5.1±1.1 (3.9- 5.9)	5.1±1.25 (3.5-7.6)	2 (20 %)	0 (0 %)
Vecuronium	(n=27)	52±23.3 (20-90)	56±33.6 (23-128)	5 (19 %)	1 (20 %)
TOF ≥70 %	(n=25)	52±22.1 (20-90)	56±33.6 (23-128)	4 (16 %)	1 (25 %)
TOF <70 %	(n= 2)	80, 30	(–)	0 (0 %)	–

Data are mean ± SD (range). The number of patients (%) with pre-existing respiratory disease (Total) and the number of these patients (%) who developed postoperative pulmonary impairment (i.e. hypoxemia alone, hypercapnia alone, or both together, according to last the column "Total" in Table 4) in the pancuronium and vecuronium groups and their subgroups is also given (TOF ≥70 % or <70 %). TOF – train-of-four ratio [%]. Differences between the respective pancuronium and vecuronium goups were not significant.

The frequency of postoperative pulmonary impairment did not differ between the general pancuronium and vecuronium study groups. Pancuronium patients with a TOF ratio <70 %, however, were affected more often than pancuronium patients with a TOF ratio ≥70 % (Table 3). Hypoxemia and hypercapnia were

found together in two patients in each of the pancuronium subgroups, and in one vecuronium patient with a TOF ratio ≥70 %. Only one of the pancuronium patients exhibited remarkable relaxometric, clinical and respiratory symptoms simultaneously (TOF ratio: 40 %; head-lift test: 2 s; post- vs. pre-operative difference in SpO_2 levels: 6 %; SaO_2: 88 %; $paCO_2$: 52.4 mm Hg).

As is shown in Table 4, pancuronium patients with a TOF ratio <70 % showed significantly higher rates of impaired pulmonary function after both types of anesthesia than those with a TOF ratio ≥70 % ($p<0.05$). Thus, the rate of postoperative pulmonary impairment was not affected by the type of anesthesia.

Fentanyl doses of all pancuronium patients as well as of all vecuronium patients were within the same corresponding ranges, independent of postoperative pulmonary status. The incidence of pre-existing respiratory diseases, in particular chronic bronchitis with productive cough associated with nicotine abusus of >20 cigarettes/day for several years, was comparable in the general pancuronium and vecuronium study groups, as well as in the pancuronium subgroups. Thus, neither fentanyl nor the presence of pre-existing respiratory diseases influenced postoperative pulmonary function (Table 5).

Discussion

The results of the present study indicate that patients receiving pancuronium were affected by PORP about 3 times more often (20 %) than patients receiving vecuronium (7 %). Only one third of the patients with a TOF ratio <70 % were detected clinically by the head-lift test. These rates are comparable to those found by other authors (Andersen *et al.* 1988, Bevan *et al.* 1988, Howardy-Hansen *et al.* 1989, Pedersen *et al.* 1992, Pedersen 1994). However, the finding that pancuronium patients with PORP exhibited a significantly higher incidence of hypoxemia, compared to pancuronium patients without PORP directly after admission to the recovery ward contradict the data published previously. Furthermore, there was a tendency to a higher incidence of hypercapnia in pancuronium patients with PORP than in those without PORP.

Berg *et al.* (1997) recently found indications that the long-acting neuromuscular blocking agent pancuronium may increase the risk of postoperative hypoxia. These authors attributed the higher incidence of pulmonary impairment in patients receiving pancuronium compared to patients receiving intermediate-acting muscle relaxants to the fact that pancuronium was used for longer-lasting surgery requiring more prolonged neuromuscular blockade. This may have resulted more frequently in the postoperative residual neuromuscular blockade (Pedersen *et al.* 1992, Berg *et al.* 1997). This is in agreement with the main findings of the present study, in which patients receiving pancuronium for lengthy surgical procedures, who showed a TOF ratio <70 %, exhibited a particularly high incidence of impaired pulmonary function after admission to the recovery ward.

PORP is apparently associated with a potential impairment of pulmonary function in the immediate postoperative period. It is therefore conceivable that patients with reduced respiratory reserves may be particularly at risk (Beemer and Rozental 1986, Pedersen *et al.* 1992). There are also indications that the ventilatory response to hypoxemia is reduced (Eriksson *et al.* 1992) and that functional impairment of muscles of the pharynx and upper esophagus may be involved (Eriksson *et al.* 1995). However, a TOF ratio <70 % does not necessarily lead to inadequate pulmonary function. Substantial impairment of neuromuscular transmission is necessary in patients with normal pulmonary function before respiratory parameters deteriorate. In this context, TOF ratios between 25 % and 45 % have been regarded as critical (Beemer and Rozental 1986). It is therefore difficult to establish a clear cause-and-effect relationship between neuromuscular and respiratory parameters of function. This is supported by studies which did not report a significant relationship between the frequency of postoperative hypoxemia and hypercapnia, and TOF ratios <70 % or related clinical signs (Pedersen *et al.* 1992, Pedersen 1994). Similarly, impairment of pulmonary function in the present study was detected in residually curarized pancuronium patients as well as in pancuronium and vecuronium patients with a TOF ratio ≥70 %. This is probably due to a number of factors which had been discussed previously as potentially intensifying the degree of PORP or leading directly to pulmonary impairment, such as pre-existing pulmonary diseases, types and sites of surgery, types and duration of anesthesia, residual effects of opiates, drug interactions or even pain responses of individual patients (Beemer and Rozental 1986, Duncan and Cohen 1987, Miller 1989, Pedersen *et al.* 1990, 1992, Pedersen 1994). Some of the factors investigated in this study (types of anesthesia, fentanyl doses, and pre-existing respiratory diseases) were comparable in the pancuronium and vecuronium

groups, and the pancuronium subgroups. Therefore, it was not these factors but rather PORP which may have been responsible for this particularly high incidence of hypoxemia and/or hypercapnia in the immediate postoperative phase after the use of pancuronium.

In a current study, both oxygenation (SpO_2, SaO_2) and ventilation ($PaCO_2$) of patients were determined, in order to document and assess the complete postoperative respiratory status. It should be noted, however, that $PaCO_2$ is a less reliable indicator of PORP as compared to the parameters of oxygenation. Eriksson *et al.* (1993) showed that moderate degrees of residual neuromuscular block do not influence the sensitivity of chemoreceptors to CO_2, while they decrease the sensitivity to hypoxia. This may help to explain, why hypoxemia was more frequent than hypercapnia in our study. In addition, this may suggest that patients with PORP are more at risk from hypoxemia than from hypercapnia.

The results of the present study as well as those of other studies (Andersen *et al.* 1988, Bevan *et al.* 1988, Howardy-Hansen *et al.* 1989) show that a routine reversal of neuromuscular block cannot reliably prevent PORP. The neostigmine dosage applied in our study was in the lower range of that routinely used in international practice, however, in the upper range for vecuronium employed in Germany (Osmer *et al.* 1996). It is generally considered that, although pancuronium and vecuronium are antagonized with equal effectiveness by neostigmine, pancuronium has a longer recovery phase than vecuronium (Gencarelli and Miller 1982). It is therefore probable that PORP could still be demonstrated in pancuronium patients in the recovery ward, but had already substantially subsided in vecuronium patients.

The reliability of clinical tests, especially the head-lift test, for detecting residual paralysis has been the subject of considerable discussion (Brand *et al.* 1977, Viby-Mogensen *et al.* 1979, Andersen *et al.* 1988, Beemer and Rozental 1986, Bevan *et al.* 1988, Engbaek *et al.* 1989, Howardy-Hansen *et al.* 1989, Pavlin *et al.* 1989, Pedersen 1994, Fawcet *et al.* 1995). The results of the present study indicate that the assessment of neuromuscular function *via* clinical criteria alone is often unreliable: Only 4 of the 12 patients with PORP were detected by the head-lift test. This confirms the findings of others (Beemer and Rozental 1986). It should, therefore be kept in mind that routine procedures of antagonism as well as evaluation of neuromuscular function by clinical parameters do not necessarily ensure the exclusion of PORP.

The present study was limited to the immediate postoperative phase. The study could therefore provide a "snapshot" of information concerning a negative effect of PORP after pancuronium on pulmonary function directly after admission to the recovery ward. However, the data do not permit a prediction whether PORP alone or together with other factors has a long-term effect on postoperative pulmonary morbidity and mortality. Such long-term effects were recently demonstrated by Berg *et al.* (1997) in a longitudinal study which showed that residual paralysis caused by pancuronium is a risk factor for postoperative pulmonary complications such as pneumonia and/or atelectasis.

In summary, PORP after pancuronium is a significant risk factor for hypoxemia and may also increase the incidence of hypercapnia immediately after admission of patients to the recovery ward. Routine practices of antagonism and/or the application of clinical tests such as the head-lift test are often unreliable and can lead to a false sense of security. In order to reduce the risk of postoperative impairment of pulmonary function, monitoring of neuromuscular function using appropriate equipment is recommended, especially when long-acting muscle relaxants such as pancuronium are administered.

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