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The Effects of Pipecuronium Bromide on Intracranial Pressure and Cerebral Perfusion Pressure

Giovanni Rosa, Maria Sanfilippo, Paolo Orfei, Giacomo Di Giugno, Vincenzo Vilardi, Piero A. Oppido, and Alessandro Gasparetto

Department of Anesthesiology and Intensive Care, State University of Rome "La Sapienza," Rome, Italy

Summary: Twenty patients with expansive pathologic intracranial lesions, who were anesthetized with thiopental, nitrous oxide in oxygen, and fentanyl and mechanically ventilated to ensure normocarbia, received pipecuronium bromide 70 μg/kg i.v. Intracranial pressure (ICP), heart rate, arterial pressure, central venous pressure (CVP), EKG, and end-tidal CO_2 were simultaneously recorded for 5 min before and for 15 min after administration of the muscle relaxant. No statistically significant changes in ICP and cerebral perfusion pressure were observed after administration of pipecuronium bromide. Cardiovascular stability was maintained during the study period except for a small, although significant, decrease of the CVP from 5.7 ± 2.5 (SEM) to 5.0 ± 2.5 mm Hg. These results, together with the long-lasting muscular effect of pipecuronium bromide, suggest that this new neuromuscular blocking agent may be used for muscle relaxation during neurosurgical operations in patients who have normal intracranial pressure at the time of administration of the drug. **Key Words:** Muscular relaxants—Pipecuronium—ICP—CPP.

Pipecuronium bromide is a new, long-acting, bisquaternary, nondepolarizing neuromuscular blocking agent. The structural modifications introduced in the pancuronium molecule (piperazine rings attached at positions 2 and 16 of the steroid nucleus) have been designed to improve its specificity, i.e., to leave its neuromuscular effect intact while reducing its nicotinic side effects (1).

Like the effects of vecuronium but unlike those of pancuronium, which causes tachycardia and blood pressure elevations, the cardiovascular effects of pipecuronium are reported as being minimal (2,3). A dose of 70 μg/kg may be expected to provide good intubating conditions in 3 min, with a clinical duration of approximately 1 h (3).

We report here the results of a study on the effects of pipecuronium on intracranial pressure (ICP), cerebral perfusion pressure (CPP), and such cardiovascular variables as heart rate (HR), systemic arterial blood pressure (BP), and central venous pressure (CVP) in neurosurgical patients during general anesthesia.

MATERIALS AND METHODS

Twenty ASA physical status I–II adult patients (age, 23–75 years) who had intracranial tumors of more than 3 cm in diameter on computerized tomography (CT) scan along with papilledema, and who were undergoing neurosurgical operations un-

Address correspondence and reprint requests to Dr. Giovanni Rosa at Istituto di Anestesia e Rianimazione, Università "La Sapienza," Viale del Policlinico, 00161 Rome, Italy.

TABLE 1. *Patient data*

Patient no.	Sex	Age (yr)	ASA	Intracranial pathology
1	M	41	1	Left parietal glioblastoma
2	M	75	2	Left frontotemporal meningioma
3	F	62	1	Left posterior parietal meningioma
4	M	28	1	Right thalamic glioblastoma
5	M	55	1	Right temporal glioblastoma
6	M	41	2	Left frontal metastasis
7	F	43	1	Left sphenoidal ridge meningioma
8	F	32	2	Right parietooccipital oligodendroglioma
9	M	48	1	Right tuberculum sellae meningioma
10	M	44	1	Right parietooccipital hemorragic glioma
11	M	23	1	Right frontal abscess
12	F	72	2	Right frontal metastasis
13	M	75	2	Right occipital parasagittal meningioma
14	F	28	1	Left temporal cystic astrocytoma
15	F	67	1	Right parietooccipital meningioma
16	F	29	1	Left rolandic astrocytoma
17	F	63	1	Left parietal parasagittal meningioma
18	M	50	2	Left posterior parietal astrocytoma
19	M	75	2	Right parietal metastasis
20	F	63	1	Left temporoparietal glioblastoma

der general anesthesia, were included in this study (Table 1). All patients gave informed consent, and the study was approved by the Human Experimental Review Committee of the Anesthesia and Resuscitation Department of the University of Rome, "La Sapienza."

Premedication consisted of atropine, 0.01 mg/kg, and phenobarbital, 1.5 mg/kg, given i.m. approximately 45 min before the operation. Anesthesia was induced with thiopental, 5 mg/kg, and maintained with 60% N_2O in O_2 and fentanyl, 0.01 mg/kg/h. Tracheal intubation was performed after a bolus injection of vecuronium, 0.1 mg/kg.

All patients were placed in the supine or lateral position with the head elevated 15° to facilitate venous drainage. All were mechanically ventilated to ensure normocarbia ($PaCO_2$, 36.3 ± 2.2 mm Hg).

Invasive BP and CVP were recorded from two precalibrated transducers. ICP was measured by introducing subdurally, through the first craniotomy hole performed, a fiberoptic transducer (Postcraniotomy Subdural Pressure Monitoring Kit, model 110 AG), calibrated prior to insertion and connected to a 420 Digital Pressure Monitor (Camino Laboratories, San Diego, CA, U.S.A.). To calculate CPP, ICP, and BP, transducers were zeroed at head level.

At least 45 min after vecuronium injection and when all the measured parameters were stable, a dose of 70 μg/kg of pipecuronium bromide dissolved in 10 ml of saline solution was administered i.v. over 5 s. Train-of-four responses were monitored to confirm that the neuromuscular action of vecuronium had completely ceased and that pipecuronium neuromuscular blockade was sufficient (with no more than one residual twitch).

Recording was begun 5 min before injection of pipecuronium to provide baseline data and was continued for 15 min afterward. During the study, the neurosurgical operation was interrupted, and it was continued at the end of the recording period.

Mean values of BP, CVP, ICP, and HR were displayed on monitors during the investigation. Cerebral perfusion pressure was calculated by the usual formula: CPP = MAP − ICP, where MAP is the mean arterial pressure.

Analysis of variance (ANOVA) was applied to evaluate the statistical significance of the variations of the parameters studied; $p \leq 0.05$ was considered statistically significant.

RESULTS

The results and statistical data are represented in Tables 2 and 3. Variations in cardiovascular values are summarized as mean ± SEM.

The administration of pipecuronium did not result in modification of the HR or MAP, although it sig-

TABLE 2. *Cardiovascular response to pipecuronium*

	HR (b/min)					MAP (mm Hg)					CVP (mm Hg)				
	0	3	5	10	15	0	3	5	10	15	0	3	5	10	15
Mean	73.0	72.3	71.0	71.2	72.5	84.3	83.9	83.1	82.4	83.4	5.7	5.4	5.3	5.0	5.0
SEM	6.1	6.7	9.0	8.0	6.2	7.3	8.3	7.3	7.9	7.3	2.5	2.6	2.6	2.6	2.5
F				2.1	NS				1.5	NS			7.6		$p < 0.01$

Values are before and 3, 5, 10, and 15 min after administration of pipecuronium, 70 μg/kg.

nificantly ($p < 0.01$) decreased the CVP from 5.7 ± 2.5 to 5.0 ± 2.5 mm Hg (Table 2). The initial ICP was, in all cases, within the normal range (mean value, 7.2 ± 3.5 mm Hg), and in no case did pipecuronium increase the ICP. Cerebral perfusion pressure was not affected by the administration of pipecuronium (Table 3).

No side effects of any nature were observed.

DISCUSSION

Transient, though not always trivial, increases in ICP occasionally occur in patients treated with succinylcholine (4) and *d*-tubocurarine (5). These increases were recently judged of minimal clinical importance (6). Nevertheless, we consider it worthwhile to evaluate the effects of new drugs on ICP and CPP, before their introduction into routine neuroanesthesiological practice, where it is preferable to choose drugs previously found not to have potentially dangerous effects on intracranial dynamics.

It has been clearly proven that pancuronium (7,8), vecuronium (9,10), and atracurium (8,11–13) all exert negligible, if any, effects on ICP. However, none of these may be considered an ideal muscle relaxant for neuroanesthesia. Pancuronium is associated with a high incidence of tachycardia and increased blood pressure (14), which may be undesirable in neurosurgical patients who have altered in-

TABLE 3. *Intracranial responses to pipecuronium*

Patient no.	ICP (mm Hg)					CPP (mm Hg)				
	0	3	5	10	15	0	3	5	10	15
1	3	3	3	3	3	77	77	77	77	77
2	12	12	11	12	12	78	78	69	68	64
3	3	2	3	3	3	82	83	82	82	82
4	5	5	4	5	5	61	58	62	58	65
5	9	9	9	9	9	87	87	87	87	81
6	4	4	4	4	4	79	79	72	76	76
7	3	2	2	3	3	80	81	78	80	80
8	7	7	7	6	7	76	76	76	67	66
9	12	12	12	12	11	71	71	74	71	70
10	14	13	13	13	14	66	67	67	67	66
11	8	8	8	8	8	79	79	79	75	79
12	7	7	7	7	7	70	63	66	66	73
13	10	10	9	10	10	67	67	68	67	67
14	12	12	12	11	12	86	86	81	82	88
15	8	8	8	8	8	89	89	89	89	89
16	5	4	5	5	5	80	83	82	82	85
17	4	4	4	3	4	81	81	81	82	81
18	7	7	7	7	7	76	81	80	80	81
19	10	10	10	10	10	69	66	69	66	69
20	2	2	2	2	2	87	86	83	86	85
Mean	7.2	7.0	7.0	7.0	7.2	77.0	76.9	76.1	75.4	76.2
SEM	3.5	3.6	3.4	3.4	3.4	7.5	8.5	7.2	8.4	7.9
F				2.1	NS				1.3	NS

Values are before and 3, 5, 10, and 15 min after administration of pipecuronium, 70 μg/kg.

tracranial dynamics. Vecuronium administration, on the other hand, sometimes induces bradycardia (15).

Atracurium may release histamine into the circulation (16), although in lower quantities than released by *d*-tubocurarine. However, some authors consider these amounts sufficient, in some patients, to produce deleterious hemodynamic effects, such as arterial hypotension and tachycardia (17). Beemer et al. recently reported an increased rate of postoperative seizures after anesthesia with isoflurane and atracurium (18). In fact, atracurium is metabolized to laudanosine, a potential epileptogenic agent (19).

Furthermore, the recovery time from neuromuscular blockade induced by either vecuronium or atracurium is quite short. Thus, frequent administration and meticulous monitoring are required to avoid sudden intraoperative movement or coughing.

In the present study, the effects of the i.v. administration of 70 μg/kg of pipecuronium bromide on ICP and CPP, as well as on BP, HR, and CVP, were studied.

We have been using fiberoptic intracranial transducers for several years with satisfactory results. In addition to our own experience, others have reported that the recordings from fiberoptic transducers in the subdural space correlate well with those from a contralateral fluid-filled ventricular catheter over a wide range of ICP (20,21).

As demonstrated by this and other studies, pipecuronium does not produce clinically significant variations in the cardiovascular parameters (2,3), nor does pipecuronium release histamine into the circulation (22). The importance of hemodynamic stability in patients who have diminished intracranial compliance has already been emphasized (23).

In our patients, the administration of pipecuronium was associated with a slight but significant decrease of the CVP. This effect can be expected from a muscle relaxant, which increases the pooling of venous blood in the muscles and decreases the mean intrathoracic pressure (24). The slight decrease, however, can be considered clinically irrelevant, since it did not significantly affect intracranial dynamics.

In our study, pipecuronium did not alter ICP or CPP in 20 patients who had bulky intracranial tumors and papilledema. Even though all patients studied had large space-occupying lesions (>3 cm in diameter) and presented with papilledema at preoperative neurological examination, the ICP measured before the administration of pipecuronium was within normal range. The low ICP is most likely due to improved cerebral compliance after anesthesia. This result also emerged in our previous studies (10,11) and may be an inherent limitation of the method. However, it would be neither correct nor wise to study the effects of a new drug directly in patients with defective intracranial compliance.

The findings of this study, coupled with the long duration of action of pipecuronium, suggest that this neuromuscular blocking drug might be used safely and advantageously during neurosurgical anesthesia, at least in patients whose ICP is normal at the time of administration of the drug.

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