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Remifentanil bolus dose is a safe procedure to control intense noxious stimuli in hypertensive neurosurgical patients

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Patients with hypertension may be more prone to develop hypotension as a consequence of opioid administration under general anesthesia. The hemodynamic and bispectral index responses to a remifentanil bolus in neurosurgical hypertensive patients under target-controlled infusion with propofol and remifentanil are addressed.

Material/Methods: Ten healthy patients and 10 patients with diagnosed hypertension under pharmacological treatment were studied. A 2 μg/kg remifentanil bolus was administered to all patients before skin incision under target-controlled infusion with propofol and remifentanil. Mean arterial pressure, heart rate, and the area under the curve for the bispectral index of the electroencephalogram were analyzed within the groups and compared between them every 30 seconds for two minutes following the bolus.

Results: Two minutes after the remifentanil bolus, remifentanil predicted effect-site concentrations reached maximum values of 8.46±0.91 ng/ml and 9.74±1.29 ng/ml in the healthy and hypertensive patients, respectively. Both groups showed a significant decrease in mean arterial pressure, heart rate, and in the area under the curve for the bispectral index. Mean arterial pressure decreased by 17.3±10% and 24±9%, heart rate by 11.1±8% and 12±8%, and the bispectral index by 13±9.2% and 8.6±8.4% in the healthy and hypertensive patients, respectively, 120 seconds after the remifentanil bolus.

Conclusions: In a clinical situation in which high remifentanil doses may be required, hypertensive patients are expected to have hemodynamic and bispectral index responses similar to those observed in healthy patients.

key words: **hypertension • remifentanil monitoring • BIS • propofol TCI • blood pressure**

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BACKGROUND

Hypertension is very frequent in the general population and is usually associated with several factors related to lifestyle habits [1]. As a consequence, during surgical procedures anesthesiologists are often faced with hypertensive patients. Remifentanil boluses are often administered to minimize or abolish reactions to noxious stimuli, such as laryngoscopy and tracheal intubation [2,3], and is the opioid of choice during brain neurosurgical procedures [4,5]. Although high doses of remifentanil administered during propofol infusion usually cause hypotension and bradycardia [6–8], patients with hypertensive disease may be more prone to develop hypotension as a consequence of opioid administration, as suggested by the investigations of Maguire and colleagues [9]. During surgical procedures, high remifentanil doses may be necessary to prevent the sympathetic response associated with intense noxious stimulation such as head-pin placement in neurosurgical procedures [8]. It is of clinical importance to evaluate the hemodynamic responses of hypertensive patients to opioid administration in order to know what hemodynamic reaction is to be expected in these patients in situations where high doses of opioids are required. Many antihypertensive treatments have the goal of reducing vasoconstriction [10] in order to decrease the high vascular resistances usually associated with hypertension [11]. This clinical situation may minimize the systemic compensatory vasoconstriction as a consequence of the remifentanil-induced reduction of cardiac function [6]. We proposed to analyze the hemodynamic and electroencephalographic responses to a remifentanil bolus in hypertensive neurosurgical patients during total intravenous anesthesia with propofol and remifentanil.

MATERIAL AND METHODS

Patients

After Research Committee approval and informed consent, two groups of ten patients with body mass indexes* below 25.8 for women and 26.4 for men submitted to consecutive neurosurgical procedures were enrolled in this study: healthy patients (group 1) and patients with diagnosed hypertension under pharmacological treatment (group 2). Medication for hypertension was not interrupted before surgery. The patients were selected according to consecutive scheduled neurosurgical procedures. Patients with advanced cardiac, pulmonary, hepatic, or renal dysfunction or under medications influencing the central nervous system were excluded. All patients were pre-medicated with 10 mg of diazepam per os two hours before entering the surgery room.

Monitoring and equipment

A peripheral venous line was inserted in the forearm of each patient and connected to a ramp of three stopcocks. An anti-reflux system was connected to the ramp in which two lines delivered propofol 1% (Fresenius Kabi, Bad Homburg, Germany) and remifentanil (Ultiva®; GSK, Midllesex, UK) at a concentration of 20 μg/ml to the patient using two Asena Alaris GH syringe pumps (Alaris Medical Systems, San Diego, CA, USA). Other needed medication and fluids were administered in a separate venous line. Sodium chloride was administered to provide a continuous infusion rate of 400 ml/h by an Infusomat infusion pump (B. Braun, Melsungen, AG, Germany). A catheter was placed in the left radial artery for invasive hemodynamic monitoring in the patients submitted to brain surgery. Patients subjected to spinal surgery had continuous noninvasive blood pressure monitoring during the study period.

Hemodynamic and carbon dioxide partial pressure ($PPCO_2$) data were collected every 5 seconds using an AS/3 Datex monitor (Datex-Ohmeda, Helsinki, Finland). The bispectral index of the electroencephalogram (BIS) data were collected every second from an Aspect Medical A-2000XP BIS monitor (Aspect Medical Systems, Newton, MA, USA) using a cutaneous electrode placed according to the manufacturer's instructions (Aspect Medical Systems, Newton, MA). Signal quality index and suppression ratio were monitored continuously.

RugLoop II® software, developed by Tom De Smet (Demed Engineering, Temse, Belgium) and Michel Struys (Ghent University, Gent, Belgium), with the Minto et al. [12,13] and Schnider et al. [14] target-controlled infusion pharmacokinetic models for remifentanil and propofol, respectively, was used to control the syringe pumps and to collect data from the BIS and Datex AS/3 monitors and from the syringe pumps, all connected to a personal computer via an RS-232 interface.

Clinical protocol

Induction of anesthesia was performed by a propofol continuous infusion rate of 200 ml/hr until loss of consciousness. At loss of consciousness, the propofol infusion was changed to the predicted effect-site concentration observed at loss of consciousness in each patient. Remifentanil was started with a plasma target concentration of 2.5 ng/ml in order to allow a progressive increase in remifentanil plasma concentration and avoid a remifentanil overshoot that would occur if the effect-site target were selected instead in a remifentanil-free patient. This was followed by 1 mg/kg intravenous rocuronium and tracheal intubation. The patients were mechanically ventilated with air + O_2. After intubation, propofol effect-site concentrations were adjusted to a BIS target level of 40 to 60 and the remifentanil plasma target was changed to the effect-site target to allow a faster drug equilibration between the plasma and the effect-site (the brain) and, consequently, a shorter delay in clinical response. Remifentanil effect-site concentrations were increased or decreased to maintain heart rate and mean arterial pressure within ±20% of the baseline values before the induction of anesthesia.

After completing the necessary preparatory procedures for neurosurgery, the patients were not stimulated to allow BIS values to stabilize and the propofol and remifentanil target concentrations were maintained unaltered for a minimum period of five minutes before the remifentanil bolus. At time zero (T0) and before skin incision, a 2 μg/kg remifentanil bolus in a saline solution concentration of 20 μg/ml was administered at 1200 ml/h using the syringe pump controlled by the RugLoop II® software. The data were analyzed during the two minutes prior to and after the remifentanil bo-

* National Health and Nutrition Examination Survey.

Table 1. Demographic and clinical data of the patients in group 1 (healthy patients) and group 2 (hypertensive patients) before induction of anesthesia.

	Age (years)	Weight (kg)	Height (cm)	BMI	LBM	ASA	Gender (F/M)	HR (bpm)	MAP (mmHg)
Group 1	48.2±14.1 (30–73)	61±7.6	162±7	23.3±2.1	44.6±5.5	I–II	9/1	71±11	93.5±6.8
Group 2	59.7±10.2 (47–74)	60.6±9.3	157±6	24.5±2.5	43.3±5.8	II	8/2	78±8	114.2±10.4*

BMI – body mass index; LBM – lean body mass; ASA – American Society of Anesthesiology guidelines for preoperative assessment; HR – heart rate; MAP – mean arterial pressure. MAP was significantly higher in group 2 (*P<0.0001).

lus; no stimulus was applied at any time. Skin incision was performed two minutes after the remifentanil bolus and the surgery proceeded.

Statistical analysis

Mean arterial pressure, heart rate, $PPCO_2$, and remifentanil and propofol predicted effect-site concentrations were compared within and between groups. Data were analyzed at baseline (values recorded immediately before the remifentanil bolus) and at 30 (T30), 60 (T60), 90 (T90), and 120 (T120) seconds after the remifentanil bolus.

For the BIS values (recorded every second), the area under the curve was calculated for all patients for each 30-second period before (120–90, 90–60, 60–30, and 30–0 seconds) and after (0–30, 30–60, 60–90 seconds, and 90–120 seconds) the remifentanil bolus. The trapezoidal rule was used to determine the area under the BIS curve for each sampling period. The average between two consecutive measurements multiplied by the time interval between them (one second) was used to obtain 30 isolated areas under the curve. These values were summed to obtain a single area under the curve for each 30-second period. The four areas under the curve before the bolus were averaged to a single value per patient: the area under the curve basal (baseline for BIS) [8].

The data were tested for normal distribution and homogeneity of variance using the Shapiro-Wilk normality test and Levene's test, respectively. ANOVA for repeated measurements with Bonferroni confidence interval adjustment for pair-wise comparisons (normal distribution and homogeneity of variance assumed) or Kruskal-Wallis analysis of variance (normal distribution or homogeneity of variance not assumed) and the Wilcoxon test (nonparametric data) were used for data analysis. Demographic data were compared between groups using analysis of variance for age, weight, and height and the chi-squared test for gender. The statistical analysis was performed using SPSS v. 13.0 for Windows. Data are expressed in the mean ±*SD*. P<0.05 was considered statistically significant.

Results

The demographic, surgery, and hemodynamic data of the patients in both groups before the induction of anesthesia are shown in Table 1. No significant differences were observed in demographics between the two groups. The mean arterial pressure was significantly higher (P<0.0001) in the hypertensive patients when awake (Table 1). Prior to the remifentanil bolus, mean arterial pressure was significantly higher in the patients with hypertension (P<0.01). The other variables were similar between the two groups (Table 2).

During the study period (two minutes before and after the remifentanil bolus), the propofol predicted effect-site concentrations remained unchanged and were similar between the groups. Two minutes after the remifentanil bolus, the remifentanil predicted effect-site concentrations reached 8.46±0.91 ng/ml in the healthy patients and 9.74±1.29 ng/ml in the patients with hypertension (Table 2).

In the two minutes after the remifentanil bolus, the healthy and hypertensive patients showed a similar significant decrease in BIS (13±9.2% vs. 8.6±8.4%, P=0.192), mean arterial pressure (17.3±10% vs. 24±9%, P=0.118), and heart rate (11.1±8% vs. 12±8%, P=0.774) (Table 2). The area under the curve for BIS decreased in both groups 90–120 seconds after the remifentanil bolus, when the remifentanil predicted effect-site concentrations reached their maximum value (Figure 1). $PPCO_2$ decreased by 0.8 mmHg in the hypertensive patients (Table 2) which, although statistically significant, cannot be considered clinically relevant.

Discussion

The hypertensive patients required higher remifentanil predicted effect-site concentrations than the healthy patients to maintain mean arterial pressure values within a ±20% interval compared with the values before the induction of anesthesia. The hypertensive and healthy patients showed similar hemodynamic and electroencephalographic responses to a 2 µg/kg remifentanil bolus, but the hypertensive patients had higher mean arterial pressure values during the entire study despite also having higher remifentanil predicted effect-site concentrations. All the patients in both groups were under similar depth of anesthesia as assessed by the bispectral index of the electroencephalogram and the similar propofol concentrations.

Sato and colleagues [15] reported a depression of cardiovagal reflex function following induction of anesthesia with propofol, and that full recovery of the cardiovagal reflex only occurred 60 minutes after stopping the propofol infusion. Propofol depression of the cardiac baroreflex control and its sympathoinhibition and impaired reflex activation of the sympathetic nervous system during hypotension [16,17] seem to provide a suitable milieu that accentuates the hemodynamic depression of the opioids by minimizing or preventing the reflex tachycardia and sympathetic responses to hypotension.

Table 2. Propofol and remifentanil predicted effect-site concentrations, bispectral index, mean arterial pressure, heart rate, and carbon dioxide partial pressure of healthy patients and hypertensive patients at baseline and 30 (T30), 60 (T60), 90 (T90), and 120 (T120) seconds after the remifentanil bolus.

		Baseline	T30	T60	T90	T120
PropCe	Healthy	2.69±0.63	2.69±0.63	2.69±0.63	2.69±0.63	2.69±0.63
	Hypert.	2.73±0.99	2.73±0.99	2.73±0.99	2.73±0.99	2.73±0.99
RemiCe	Healthy	1.24±0.65	5.11±0.72	8.03±0.64	8.74±0.76	8.46±0.91
	Hypert.	2.22±1.16*	5.86±1.32	8.73±1.23	9.73±1.24	9.74±1.29*
BIS	Healthy	43.5±6.4	44.6±8.9	43.7±8.1	39.8±7.8	37.5±7.4#
	Hypert.	44.2±6.3	44.0±6.9	42.6±6.2	39.8±6.2	40.4±6.9#
MAP	Healthy	85.4±11.1	85.9±11.5	80.9±13.7	73.9±13.6	70.9±14.5##
	Hypert.	108±18.5**	106.6±17.2	99.4±12.9	87.7±11	81.1±14.1##
HR	Healthy	73±18.1	73.3±17.7	68.2±12.7	66.7±15.1	64.2±13.7##
	Hypert.	74.5±10.1	73.4±10.1	70.5±9.7	66.6±10.3	65.5±11.6##
$PPCO_2$	Healthy	32.2±4.6	32.2±4.6	32±4.7	32±4.5	31.7±4.4
	Hypert.	31±2.2	30.9±2.2	30.8±2.2	30.6±2.2	30.2±2.2#

PropCe (μg/ml) – propofol predicted effect-site concentrations; RemiCe (ng/ml) – remifentanil predicted effect-site concentrations; BIS – bispectral index of the electroencephalogram; MAP (mmHg) – mean arterial pressure; HR (bpm) – heart rate; $PPCO_2$ (mmHg) – carbon dioxide partial pressure. Comparisons with baseline within the groups: #$P<0.05$ and ##$P<0.0001$. Comparisons between the groups: *$P<0.05$ and **$P<0.01$.

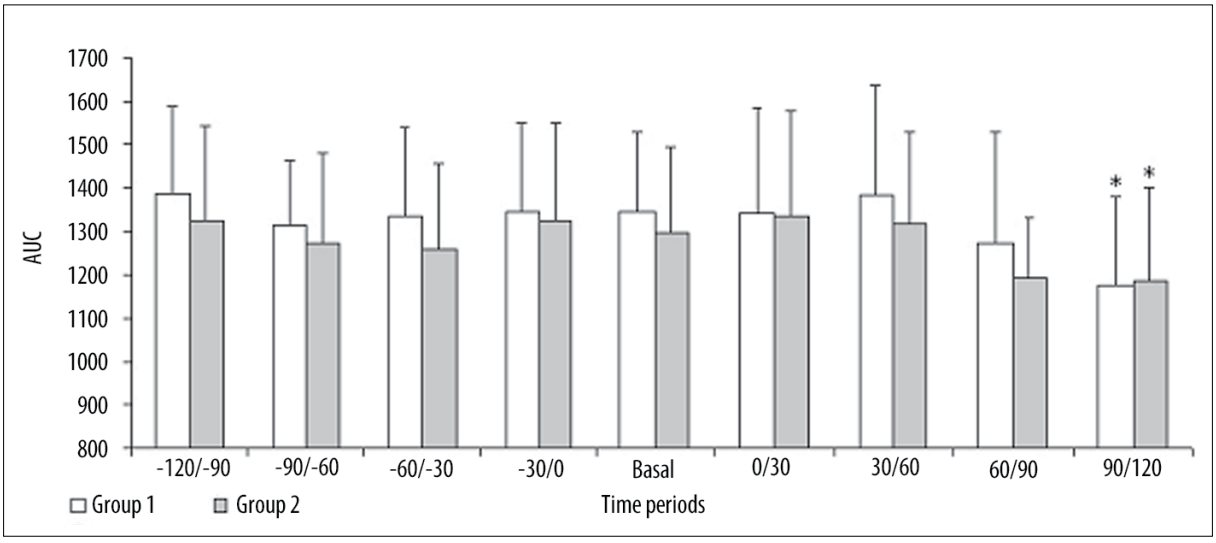

Figure 1. Area under the curve for the bispectral index of the electroencephalogram with standard deviation in the 30-second periods before (–120/–90, –90/–60, –60/–30, –30/0) and after (0/30, 30/60, 60/90, 90/120) the remifentanil bolus. Group 1 – healthy patients; group 2 – hypertensive patients. *$P<0.05$ compared with the area under the curve for basal. No differences were observed between the groups in any time period.

The vascular effects of remifentanil are not completely understood. The direct vasodilatation caused by remifentanil may be related to the remifentanil-induced decrease in arterial elastance [18] and to endothelium-mediated vasorelaxation [19]. Indirectly, the remifentanil depressive effects on systemic blood pressure are accentuated by the decrease in cardiac function, which causes further decreases in mean arterial pressure [6]. Remifentanil has several effects on the heart rate and cardiac function, but it is generally accepted that the opioid-induced bradycardia is mainly mediated by vagal activity [20]. High remifentanil doses decrease the cardiac index, stroke volume index, and heart rate, which may lead to an accentuated reduction in mean arterial pressure [6]. In our study, heart rate showed a similar decrease in both groups, which indicates that the influence of cardiac function on vasodepression was also identical. As antihypertensive therapy usually aims at reducing vasoconstriction [10], a higher hemodynamic depression would be expected in hypertensive patients. A possible explanation for the absence of a more pronounced hypotension in the hyper-

tensive patients may be related to arterial stiffness usually present in hypertensive patients [21–23]. This pathology reduces arterial elastance due to the dedifferentiation of smooth muscle cells leading to arterial wall hypertrophy [24,25], which may have reduced the direct effect of remifentanil on blood vessel walls [18,19].

The patients involved in our study were taking medication with calcium antagonists, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or β-blockers or a combination of two or more of these agents. These drugs reduce the physiological vasoconstrictive responses, inotropism, and blood volume and/or cause arterial vasodilatation and could influence the individual response to the remifentanil bolus. It is reasonable to expect that the antihypertensive medication, particularly angiotensin-converting enzyme inhibitors, could contribute to a more accentuated decrease in mean arterial pressure in the hypertensive patients [11]. However, in our study the patients with hypertensive disease under antihypertensive medication showed similar hemodynamic behavior as patients without hypertension. These findings corroborate those published by Sear and colleagues [26] and Maguire and colleagues [9], who observed that different antihypertensive monotherapies seem to have no influence on cardiovascular response in hypertensive patients.

The depressant effects of remifentanil on the bispectral index of the electroencephalogram in patients receiving propofol [7,8] may be related to an increase in propofol arterial and brain concentrations as a consequence of the reduced cardiac output usually associated to high doses of remifentanil [6,27]. The coexisting cerebrovascular diseases usually associated with hypertensive disease could affect the blood-brain dynamics and thus affect cerebral metabolism. Nevertheless, the decrease in BIS did not differ between the patients with and without hypertension.

Conclusions

High doses of remifentanil administered to hypertensive neurosurgical patients under general anesthesia with target-controlled infusion with propofol and remifentanil produces similar hemodynamic behavior as that observed in healthy patients.

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