Effects of sufentanil or ketamine administered in target-controlled infusion on the cerebral hemodynamics of severely brain-injured patients*

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Objective: **The manual injection of a bolus of opioid in patients with brain injury induces an increase in intracranial pressure related to a decrease in mean arterial pressure. Such an effect has not been observed with the use of ketamine. The use of target-controlled infusion would minimize or suppress this adverse effect of opioid. This study evaluated the effects of an increase in plasma concentrations of sufentanil or ketamine administered by target-controlled infusion on cerebral hemodynamics.**

Design: **Prospective, randomized study.**

Setting: **Intensive care unit in a trauma center.**

Patients: **Thirty patients with severe traumatic brain injury.**

Interventions: **Patients were assigned to receive sedation consisting of sufentanil-midazolam or ketamine-midazolam using target-controlled infusion. Twenty-four hours after the onset of sedation, the target concentrations of sufentanil or ketamine were doubled for 15 mins. Blood samples were collected to determine the actual plasma concentration of sufentanil and ketamine, before and 15 mins after concentration change.**

Measurements and Main Results: **The baseline values of intracranial pressure and cerebral perfusion pressure were similar in both groups. The two-fold increase in drug concentrations did not involve a significant change for intracranial pressure, cerebral perfusion pressure, and mean velocity of middle cerebral artery in both the ketamine and the sufentanil groups. The measured plasma concentrations of sufentanil and ketamine were 0.4 ± 0.2 ng/mL and 2.6 ± 2.2 μg/mL, respectively, before the increase in concentrations and 0.7 ± 0.4 ng/mL and 5.5 ± 3.8 μg/mL after.**

Conclusions: **The present study shows that the increase in sufentanil or ketamine plasma concentrations using a target-controlled infusion is not associated with adverse effects on cerebral hemodynamics in patients with severe brain injury. The use of target-controlled infusion could be of interest in the management of severely brain-injured patients. However, there is a need for specific pharmacokinetic models designed for intensive care unit patients. (Crit Care Med 2005; 33:1109–1113)**

KEY WORDS: severe head injury management; target-controlled infusion; ketamine; sufentanil; intensive care unit; intracranial pressure; cerebral perfusion pressure

An important objective in the management of severely brain-injured patients is the maintenance of a cerebral perfusion pressure of ≥60 mm Hg. The aim of sedation is to prevent intracranial hypertension due to pain or agitation. Before noxious stimuli, such as endotracheal suction, brain-injured patients require more analgesic drug to avoid transient intracranial hypertension. However, the manual administration of a bolus of opioids has been associated with a significant increase in intracranial pressure (ICP) related to a decrease in blood pressure in severely brain-injured patients under mechanical ventilation (1). Ketamine is not commonly used in severely brain-injured patients. Nevertheless, two studies show that ketamine in combination with midazolam or propofol does not affect and even may decrease ICP at higher doses in mechanically ventilated patients with decreased intracranial compliance following severe head trauma (2–4). A manual bolus of ketamine administered to the same patients has no deleterious effect on ICP and blood pressure (4). The use of target-controlled infusion (TCI) makes it possible to maintain a better degree of hemodynamic stability compared with manual administration during anesthesia (5). However, the use of TCI to provide sedation in traumatic brain-injured patients has never been investigated. One could expect to obtain an increase in plasma concentrations of analgesic drugs without deleterious cerebral hemodynamic effects for sufentanil. We used ketamine as a comparator.

The aim of this study was to compare the effects of an increase in plasma concentrations of sufentanil and ketamine, administered by TCI, on cerebral hemodynamics.

MATERIALS AND METHODS

Group Assignment. After approval by the Ethics Committee of our institution, we obtained informed consent from each patient's next of kin. Thirty patients with severe head injury were enrolled in the study after initial resuscitation. Inclusion criteria were as follows: severe traumatic brain injury resulting in a postresuscitation Glasgow Coma Scale score <9, analysis of the first computed tomography scan according to the Traumatic Coma Data Bank ≥2 (6), ICP monitoring required, and age 18–75 yrs. Patients were randomized to receive sedation with sufentanil

***See also p. 1172.**

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and midazolam in the sufentanil group or with ketamine and midazolam in the ketamine group according to a randomization table. Both drugs were administered by TCI using PaMo software (7). A syringe pump (Pilote C, Fresenius, Grenoble, France) was driven by a personal computer.

Patient Management. TCI was initiated when intracranial monitoring was required. TCI was initiated with a target plasma concentration of 0.3 ng/mL sufentanil and 100 ng/mL midazolam in the sufentanil group and of 1.0 μg/mL ketamine and 100 ng/mL midazolam in the ketamine group. Efficacy of sedation was evaluated on obtaining five criteria based on a behavioral pain scale (8) reported in Table 1. Next, predictive plasma concentrations were adjusted step by step (0.15 ng/mL for sufentanil or 0.5 μg/mL for ketamine and 50 ng/mL for midazolam) to reach these criteria.

Arterial pressure in Co_2 was maintained between 35 and 38 mm Hg. Management was in agreement with the previously published guidelines for managing patients with severe head injury (9).

Monitoring. Mean arterial pressure (MAP) was continuously monitored via an arterial catheter. Intracranial pressure measurements were obtained through a frontal ventricular catheter system with a Camino transducer (Camino V420 monitor, Camino Laboratories, San Diego, CA). From these last two variables, cerebral perfusion pressure (CPP = MAP − ICP) was continuously calculated and displayed on the monitor. Zero level was checked before use of each Camino transducer. A 2-MHz pulsed Doppler ultrasound device (Angiodine 2; DMS, Montpellier, France) was used to measure erythrocyte velocity. After identification of the right anterior cerebral artery and middle cerebral artery, the depth was adjusted by 2-mm increments to obtain signals from the proximal (M1) segment of the middle cerebral artery. The electroencephalogram was recorded continuously using an Aspect A-1000 electroencephalogram monitor (Aspect Medical Systems, version 3.12), which also computed the bispectral index (BIS) in real time. Silver/silver chloride pre-gelled electrodes (3M Red Dot 2360, Pithiviers, France) were applied to the left and right frontal (Fp1 and Fp2) regions and referred to a vertex electrode (CZ). Electrode impedance was maintained <5 kΩ.

Protocol. The experimental protocol is presented in Figure 1. Twenty-four hours after the onset of sedation, the target plasma concentrations of sufentanil or ketamine were doubled. Target plasma concentrations of midazolam were unchanged during the entire protocol. Since requirements in sedation differ for individual patients, we chose to perform a two-fold increase in sufentanil or ketamine plasma concentrations to standardize the effects on cerebral hemodynamics.

The effects of this increase in concentrations were serially evaluated on systemic (MAP) and cerebral hemodynamics by measurements of ICP, CPP, and mean velocity of middle cerebral artery (V_{MCAM}). All variables were measured every minute for 5 mins before and every minute for 15 mins after drug concentration increase. Changes in BIS were monitored during the protocol. For both groups, the variables that could have affected ICP and CPP were recorded: arterial hemoglobin oxygen saturation, end-tidal fraction in Co_2, and body temperature. We noted requirements in fluid replacement or vasopressor for maintaining blood pressure.

Pharmacokinetics and Dosages. The pharmacokinetics used in TCI were from Domino et al. (10) for ketamine, Hudson et al. (11) for sufentanil, and Avram et al. (12) for midazolam.

Two arterial blood samples were obtained to assess ketamine, sufentanil, and midazolam plasma concentrations: one 5 mins before and one 15 mins after concentration change. The concentrations of ketamine (13) and midazolam (14) were analyzed by a previously described high-performance liquid chromatography method and those of sufentanil by radioimmunoassay (15).

Statistics. Data are presented as mean ± SD. Baseline values represent an average of five measurements obtained during a 5-min period before concentrations increase. For patient characteristics, qualitative data were compared using a chi-square test, and quantitative data were compared with the Student's *t*-test for unpaired data. Physiologic measures were analyzed with a repeated-measures analysis of variance and the Newman-Keuls' test. We considered $p < .05$ as significant.

RESULTS

Patient characteristics including age, postresuscitation Glasgow Coma Scale score, Injury Severity Score, analysis of first tomography scan according to the Traumatic Coma Data Bank, and cerebral injuries are reported in Table 2. Two patients in each group underwent neurosurgery to evacuate a hematoma before protocol: one subdural and one extradural hematoma in the sufentanil group and one subdural with decompressive craniectomy and one intracerebral hematoma in the ketamine group. Three patients underwent other surgery (abdominal, orthopedics) before protocol, in each group. One patient had hemorrhagic shock in each group.

TCI was initiated 32 ± 19 hrs in the sufentanil group and 30 ± 25 hrs in the ketamine group after the trauma.

The baseline values for arterial hemoglobin oxygen saturation, end-tidal fraction in Co_2, and body temperature were similar in the two groups (Table 2). No significant changes occurred during the experiment.

Table 1. Sedation levels were adjusted to obtain five criteria

Absence of agitation
No fighting with ventilator
Relaxed facial expression
Absence of neurovegetative troubles[a]
Absence of intracranial hypertension related to nonnociceptive stimulations[b]

[a]Tachycardia, hyperventilation, hypertension; [b]external noises, lights on/off, interventions on intravascular catheters.

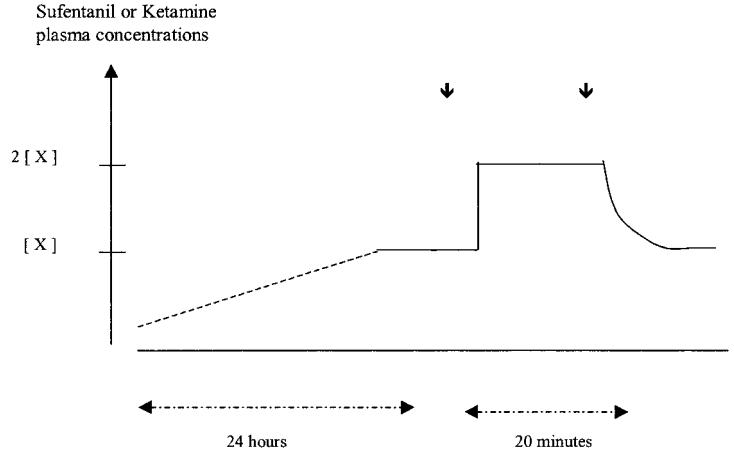

Figure 1. Experimental protocol. Sedation with target-controlled infusion was initiated when intracranial pressure monitoring was required. Plasma concentrations of sufentanil, ketamine, and midazolam were adjusted during 24 hrs according to clinical criteria. Then sufentanil or ketamine plasma concentrations were increased two-fold.

Effect on Hemodynamics. The baseline value of ICP was 17.7 ± 6.5 mm Hg (9–30 mm Hg) in the sufentanil group compared with 16.2 ± 6.4 mm Hg (9–28 mm Hg) in the ketamine group (not significant). The baseline value of CPP was not significantly different between the sufentanil and ketamine groups (80 ± 14 mm Hg vs. 85 ± 14 mm Hg, not significant). The two-fold increase in sufentanil or ketamine concentrations did not involve significant changes in MAP, ICP, and CPP compared with the baseline values (Fig. 2). No significant difference was observed between the two groups. No patient received vasopressor or fluid replacement during the experiment.

The baseline value of V_{MCAM} was significantly higher in the sufentanil group than in the ketamine group (77 ± 21 cm/sec vs. 60 ± 33 cm/sec, $p = .03$). However, no significant change was related to the two-fold increase in drug concentrations (Fig. 3*a*). The baseline value of BIS was not significantly different in the ketamine group compared with that of the sufentanil group (74 ± 20% vs. 65 ± 25%, $p = .29$). A significant difference occurred 6, 7, and 13 mins after the two-fold increase in drug plasma concentrations ($p < .05$, Fig. 3*b*).

Plasma Concentrations. At the onset of the experiment, predictive plasma concentrations of sufentanil and midazolam were 0.4 ± 0.1 ng/mL and 158 ± 75 ng/mL, respectively, for the sufentanil group. Predictive plasma concentrations of ketamine and midazolam were 1.6 ± 0.8 μg/mL and 138 ± 60 ng/mL, respectively, for the ketamine group. At these plasma concentrations, the five criteria of efficacy of sedation were obtained for all patients. Measured plasma concentrations are represented in Table 3. The ratio (concentration after increase/concentration before increase) was 1.8 ± 0.3 for sufentanil and 2.5 ± 1.9 for ketamine—this difference was not significant ($p = .23$). Measured plasma concentrations of midazolam remained unchanged in both groups during the protocol, with no significant difference.

Table 2. Patient population

	Sufentanil (n = 15)	Ketamine (n = 15)
Age, yrs, mean ± SD	29 ± 12	29 ± 11
Weight, kg, mean ± SD	75 ± 9	71 ± 18
Postresuscitation Glasgow Coma Scale, median	6	5
Traumatic Coma Data Bank, median	3	2
Injury Severity Score, median	32	29
Cerebral injuries		
Multiple contusions	9	10
Subdural hematoma	4	2
Extradural hematoma	2	1
Intraventricular hemorrhage	2	2
Subarachnoid hemorrhage	2	1
Severe edema	3	3
Body temperature, °C, mean ± SD	37.2 ± 0.9	37.1 ± 0.9
Sa_{O_2}, %, mean ± SD	99 ± 0.8	98 ± 1.3
Fet_{CO_2}, mm Hg, mean ± SD	28.4 ± 5	28.7 ± 4.3

Sa_{O_2}, arterial hemoglobin oxygen saturation; Fet_{CO_2}, end-tidal fraction in C_{O_2}.

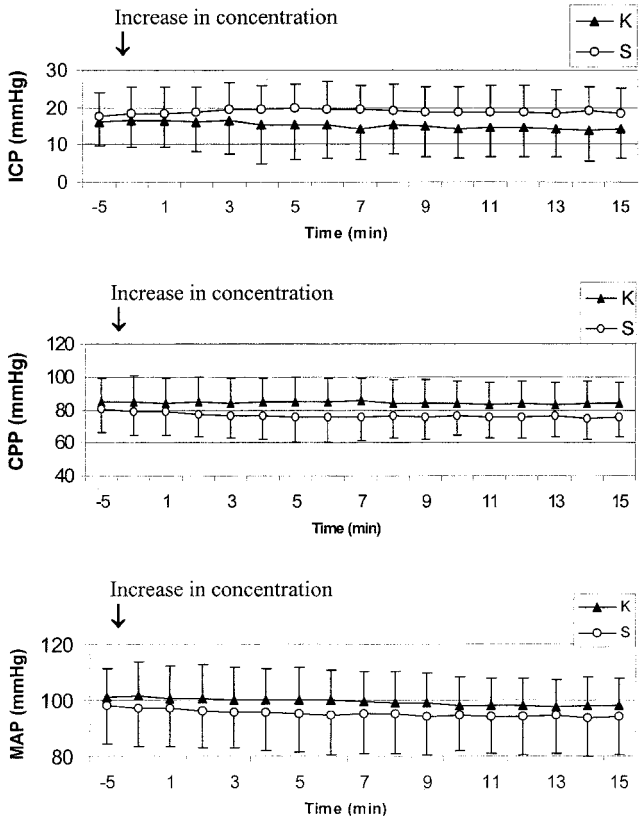

Figure 2. Mean values of intracranial pressure (*ICP*), cerebral perfusion pressure (*CPP*), and mean arterial pressure (*MAP*) after ketamine (*K*) and sufentanil (*S*) plasma concentration two-fold increase.

DISCUSSION

The present study investigated the effects of sufentanil or ketamine administered through a TCI system in patients with severe traumatic brain injury. To our knowledge, this is the first study investigating the use of TCI for sedation in such intensive care unit (ICU) patients. A two-fold increase in sufentanil or ketamine plasma concentrations administered by TCI did not induce a deleterious effect on cerebral hemodynamics.

The increase in ICP after a manual bolus of opioids is mostly related to a decrease in MAP, probably due to an activation of the vasodilatory cascade (1, 16). The possibility with the TCI system to administer opioids slowly with a significant decrease in cumulative dose should make it possible to achieve a better hemodynamic stability (5, 17). The infusion rates, which are controlled by software, depend on the duration of infusion, the pharmacokinetic properties of each drug, and patient characteristics. To apply our protocol manually, we calculated for each group the infusion rate of drugs required to achieve the same objective: the infusion rates were 95 μg/kg/min ketamine and 1.5 μg/kg/min mida-

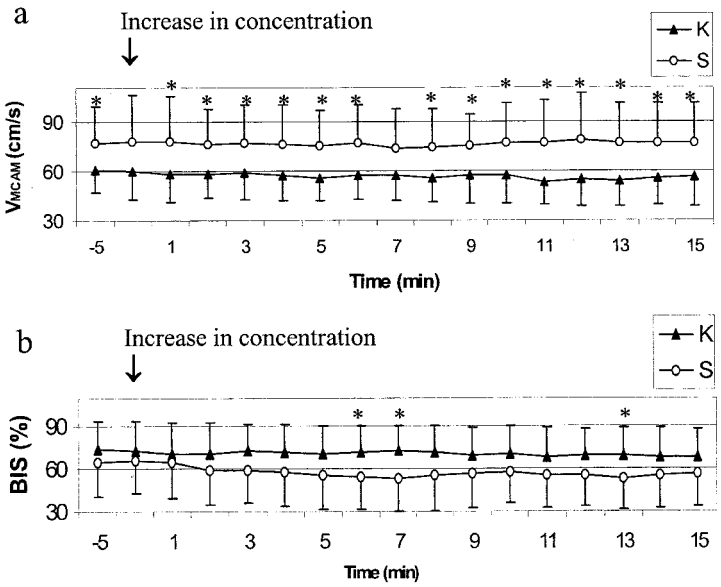

Figure 3. Mean values of mean velocity of middle cerebral artery (V_{MCAM}) and bispectral index (*BIS*) after ketamine (*K*) and sufentanil (*S*) plasma concentration two-fold increase. *$p < .05$.

Table 3. Measured and predictive plasma concentrations of the sedative drugs: one dosage 5 mins before and one dosage 15 mins after drug concentration two-fold increase

	Sufentanil Group		Ketamine Group	
	Before Increase	After Increase	Before Increase	After Increase
Sufentanil, ng/mL; ketamine, μg/mL				
Measured concentrations	0.4 ± 0.2	0.7 ± 0.3	2.6 ± 2.2	5.5 ± 3.8
Predictive concentrations	0.4 ± 0.1	0.8 ± 0.2	1.6 ± 0.8	3.2 ± 1.6
Midazolam, ng/mL				
Measured concentrations	284 ± 246	278 ± 241	232 ± 149	228 ± 143
Predictive concentrations	158 ± 75	158 ± 75	138 ± 60	138 ± 60

zolam in the ketamine group and 0.007 μg/kg/min sufentanil and 1.7 μg/kg/min midazolam in the sufentanil group. We found similar requirement in a previous study (2). The mean doses of ketamine or sufentanil that were administered to achieve a plasma concentration two-fold increase were 180 mg and 15 μg, respectively. Concerning sufentanil, this slow infusion rate could probably explain the discordance with previous studies (1) that showed a decrease in CPP related to opioid bolus administration. Actually, rapid injection of sedative agents produces significantly higher peak arterial concentrations, inducing a systemic effect (18). As opposed to bolus, a continuous infusion of sufentanil did not alter MAP and ICP (1). Werner et al. (19) emphasized the role of MAP, showing that a bolus of sufentanil did not change ICP when MAP was maintained constant by the use of a norepinephrine infusion.

Drug administration by TCI is not currently used in clinical practice for ICU patients. Most of the available models have been studied in patients undergoing surgery. There are actually few pharmacokinetic models for sedative drugs adapted to ICU patients. Significant differences in pharmacokinetic data have been observed between ICU patients and healthy volunteers; for instance, increased distribution volume, protein binding reduction, and drug clearance disturbances are frequent in ICU patients (20). To verify the accuracy of the plasma concentration two-fold increase, we collected blood and measured the concentrations of each agent. The prediction of the model was accurate for sufentanil but not for ketamine and midazolam. The performance of these last models was not designed for our population of mechanically ventilated ICU patients. Nevertheless, the two-fold increase in plasma concentrations that was predicted for the experiment was confirmed by the measured plasma concentrations for both sufentanil and ketamine.

According to the literature, ketamine and sufentanil have different effects on cerebral hemodynamics. The cerebrovascular effects of ketamine remain controversial. This drug is not commonly used in clinical practice for the sedation of brain-injured patients. Indeed, the cerebrovascular effects of ketamine depend on the preexisting cerebrovascular tone induced by the background anesthetic (21) and by other factors influencing cerebral hemodynamics such as $Paco_2$ and MAP levels. However, in several studies, the use of ketamine has been shown to be safe and effective in head-injured patients (2–4). Continuous infusion of ketamine-midazolam was as efficient as sufentanil-midazolam on ICP and CPP control in patients with severe head injury (2). Kolenda et al. (3) compared the effects of a continuous infusion of ketamine-midazolam with those of fentanyl-midazolam on ICP and CPP and reported similar results. A bolus of ketamine decreased or did not change ICP and CPP in mechanically ventilated head-trauma patients sedated with propofol (4). All these studies were carried out in mechanically ventilated patients to maintain a $Paco_2$ of approximately 35 mm Hg, and ketamine was used in combination with midazolam or propofol. The use of midazolam or propofol could limit the effects of ketamine on cerebral blood flow (21, 22). However, ketamine has an interesting profile for sedation of severely brain-injured patients, especially in case of instable hemodynamic state.

The baseline V_{MCAM} values were significantly different in the two groups. We do not have a clear explanation for this observation since such a finding was not observed in our previous study (2). Midazolam induced dose-related changes in cerebral blood flow, but the difference in measured plasma concentrations of midazolam was not significant between the ketamine and sufentanil groups (232 ± 149 and 284 ± 246 ng/mL, respectively) (23). Nevertheless the two-fold increase in ketamine or sufentanil concentrations did not induce significant changes in V_{MCAM}.

The reliability of monitoring sedation by BIS is not known in patients with traumatic brain injury. In the present study, BIS was measured to assess a difference between the two groups related to the analgesic drug. In the present study,

the BIS values were higher in the ketamine group. Such a finding is in agreement with those of previous studies in which the administration of ketamine did not affect BIS (24–26). In healthy volunteers, low to moderate doses of opioids do not change the BIS (27), but in patients with traumatic brain injury, high doses of remifentanil induce a dose-related decrease in the BIS (28). Nevertheless, BIS is not really suited to monitor sedation in ICU patients. Vivien et al. (29) showed that BIS was overestimated in ICU patients receiving sedation.

The clinical utility of TCI in severely brain-injured patients would be to decrease sedation level during nonnociceptive stimulation and increase sedation level before nociceptive stimulation without side effects on ICP and CPP meeting with manual bolus injection. In this study, we observed no side effects on ICP and CPP related to a sufentanil or ketamine plasma concentration two-fold increase by TCI. The next step will be to evaluate in further studies the effects on a noxious stimulation, such as endotracheal suction.

CONCLUSIONS

This prospective randomized study shows that a sufentanil or ketamine plasma concentration two-fold increase by TCI was not followed by any changes in ICP and CPP in patients with traumatic brain injury. This is the first study to evaluate the use of TCI in severely brain-injured patients. The administration of an opioid bolus through a TCI perfusion system could be of interest since this system makes it possible to reduce the systemic effects of opioids and to minimize their detrimental impact on cerebral hemodynamics. However, the extensive use of TCI in ICU patients is required to conceive specific pharmacokinetic models adapted to this specific population.

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