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Comparison of sufentanil with sufentanil plus magnesium sulphate for sedation in the intensive care unit using bispectral index

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Received: 19 February 2003
Revisions requested: 15 May 2003
Revisions received: 27 May 2003
Accepted: 5 August 2003
Published: 28 August 2003

Critical Care 2003, **7**:R123-R128 (DOI 10.1186/cc2365)
This article is online at http://ccforum.com/content/7/5/R123

Abstract

Introduction In intensive care unit patients we assessed, using bispectral index (BIS) monitoring, whether the addition of magnesium sulphate infusion could decrease the sufentanil infusion required to maintain sedation.

Patients and methods A total of 30 adult patients who were expected to require machanical ventilation for 6 hours in the intensive care unit were randomly assigned to receive either sufentanil infusion or sufentanil plus magnesium infusion. We monitored BIS levels continously. BIS levels in the range 61–88 are required to maintain a state of sedation, and in both groups BIS levels were kept within this range by increasing or decreasing the sufentanil infusion. Hourly consumption of sufentanil was monitored. Cardiovascular, respiratory and biochemical data were recorded.

Results There was no significant difference between the groups with respect to cardiovascular, respiratory and biochemical parameters. Magnesium infusion, when added to sufentanil infusion, decreased the consumption of sufentanil at all times accept during the first hour ($P<0.001$). There was no significant difference in BIS values between the groups ($P>0.05$).

Conclusion This is the first clinical study to demonstrate that magnesium sulphate infusion decreases sufentanil requirements. Because of the limited number of patients included and the short period of observation, our findings must be confirmed by larger clinical trials of magnesium infusion titrated to achieve prespecified levels of sedation. Furthermore, randomized clinical studies are needed to determine the effects of magnesium infusion on opioids.

Keywords bispectral index, intensive care unit, magnesium, sedation, sufentanil

Introduction

Inadequate sedation may adversely affect morbidity and even mortality in the intensive care unit (ICU), and the search for the ideal sedative agent therefore continues [1,2]. Sedation is an important part of therapy for critically ill patients in the ICU. It reduces anxiety and stress, facilitates sleep, prevents injuries and accidental removal of catheters, reduces resistance to mechanical ventilation, and decreases oxygen consumption in severe head injury [2]. Under-sedation may result in hypertension, tachycardia, discomfort and resistance to

APACHE = Acute Physiology and Chronic Health Evaluation; BIS = bispectral index; ICU = intensive care unit.

mechanical ventilation. Hypotension, bradycardia, coma, respiratory depression, immunosuppression, paralytic ileus and renal failure are among the risks associated with over-sedation [2,3]. Use of combinations of hypnotics and opiates for sedation has become common.

Bispectral electroencephalographic analysis was recently developed, and the effects of many anaesthetic agents on levels of sedation have been studied using bispectral index (BIS) monitoring. These reports suggest that BIS levels correlate well with depth of sedation [4,5]. Only a few investigators have studied the validity of BIS monitoring in ICU patients, but a correlation between BIS levels and sedation scales in ICU patients has been reported for various agents [6,7].

Sufentanil allows rapid emergence from sedation and less respiratory depression than occurs with other sedative agents, and it maintains haemodynamic stability [8]. It is an effective analgesic and its rapid onset of action allows simple titration, according to individual patient tolerance, to the the desired clinical end-point. Furthermore, its short duration of action means that the desired analgesic effect will continue for as long as the infusion is continued, and any undesirable side effects will be short-lived following discontinuation [9]. In addition, mechanically assisted spontaneous ventilation modes can safely be used under continuous sedation with sufentanil [10].

Magnesium sulphate is involved in several processes, including hormone receptor binding, gating of calcium channels, transmembrane ion flux and regulation of adenylate cyclase, muscle contraction, neuronal activity, control of vasomotor tone, cardiac excitability and neurotransmitter release. In many of its actions it has been likened to a physiological calcium channel blocker [11].

In the present study, conducted in ICU patients, we assessed (using BIS monitoring) whether the addition of magnesium sulphate infusion could decrease the sufentanil infusion required to maintain sedation.

Patients and method

Patient population and study design

The study was approved by the regional committee on medical research ethics. Written informed consent was obtained directly from the patients whenever possible, or from their next of kin.

A total of 30 adult patients (trauma, general surgical and medical) requiring mechanical ventilatory support were enrolled in this prospective analysis. The initial severity of illness was determined using Acute Physiology and Chronic Health Evaluation (APACHE) II [12] scores. Patients with overt disease affecting the brain (e.g. head trauma, intracranial haemorrhage, meningitis or stroke) and those receiving neuromuscular blocking agents were excluded.

Patients were ventilated mechanically with oxygen enriched air to achieve acceptable blood gas levels. If required, patients underwent surgical procedures before the start of the study. No invasive surgery was performed during the 24 hour study period. Ventilator settings, level of positive end-expiratory pressure and fractional inspired oxygen were kept constant during sufentanil and magnesium infusion.

Antibiotic treatment was adjusted in accordance with results of bacteriological culture, such as culture of blood or of samples taken from different sites of the body. No inotropic agent was administered during the study.

Protocol

The study was prospective, randomized, double blind, and placebo-controlled. Randomization was conducted according to a computer directed, permutated block design. In accordance with the double blind protocol, drug solutions and infusions were administered to patients by a nurse who had no knowledge of the study protocol. The BIS was monitored using a BIS Monitor Model A-2000 (Aspect Medical Systems Inc., Newton, MA, USA). After placement of the BIS electrode (Aspect Medical Systems Inc., Natick, MA, USA) above the bridge of the nose, over the temple area, and between the eye and hairline, the monitor undergoes automic impedence testing to ensure acceptable signal reception. When an inadequate signal is sensed the display's colour pattern changes, allowing easy differentiation between true and spurious values. Electrodes were repositioned or replaced if impedances increased to the extent that electroencephalographic evaluation was impaired. The degree of sedation was measured continously using BIS monitoring. Patients were maintained at BIS levels in the range 61–88, which are associated with a sedated state.

At the start of the study all patients received 1 μg/kg sufentanil by intravenous bolus. Immediately after, groups 1 and 2 received an intravenous sufentanil infusion for 6 hours, but group 2 also received an intravenous infusion of magnesium sulphate (2 g/hour) for 6 hours via a dedicated central venous catheter. Average BIS values were kept in the range 61–88 by decreasing or increasing sufentanil infusion in both groups, and hourly consumption of sufentanil was monitored. Evidence of hypocalcaemia was sought using clinical signs (Chvostek's and Trousseau's) and measurement of total serum calcium concentrations. Effects of elevated magnesium include flushing, loss of tendon reflexes, respiratory arrest, and prolongation of the PR interval and the QRS complex; these were also evaluated.

The sedative infusion was discontinued when cardiovascular and respiratory adverse events were identified, defined as a change in arterial pressure of more than 40% from baseline, bradycardia to less than 50 beats/min, or tachyarrhythmia. No other sedative or analgesic agents were given, and no patient received spinal or epidural analgesia in the ICU.

Measurements

All patients underwent placement of arterial catheters and central venous catheters via the subclavian vein. Arterial blood samples were drawn for measurements of pH, oxygen and carbon dioxide tensions, and arterial oxygen saturation (Medica Easy BloodGas; Massachusetts, USA). Central venous pressure, mean arterial pressure, heart rate and nasopharyngeal temperature were continuously monitored (SpaceLabs Inc., Redmond, USA). Sodium, potassium, calcium (Ilyre, Ion Selective Electro Analyzer; LISpA, Milan, Italy), magnesium levels (Merek Mega, Darmstadt, Germany), and bilirubin, alanine aminotransferase and creatinine (Vitalab Flexor, Dieren, The Netherlands) were determined at baseline (15 min before start of the study), immediately after sedative infusion and 24 hours after sedative infusion.

Statistics

Demographic data; haemodynamic, biochemical and arterial blood gas changes; sufentanil dose; and changes in BIS were analyzed using independent samples *t* tests. Data were expressed as means ± standard deviation. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Clinical and demographic characteristics of the patients are summarized in Table 1. Of the 30 patients included in the study, 15 received sufentanil (group 1) and 15 received sufentanil plus magnesium (group 2). Eight patients died while they were hospitalized in the ICU for reasons related to infection (four in group 1 and four in group 2). Baseline APACHE II scores (12.3 ± 4.3 and 13.4 ± 4.6 in groups 1 and 2, respectively) and central venous pressure (5.9 ± 2.4 mmHg and 5.6 ± 2.7 mmHg) were similar between groups ($P > 0.05$). The sufentanil infusion and the sufentanil plus magnesium infusion were well tolerated by all patients, and no adverse effects were noted.

Haemodynamic parameters and oxygen transport variables

There was no significant difference between the groups with respect to pH, oxygen or carbon dioxide tension, ratio of arterial oxygen tension to fractional inspired oxygen, and arterial oxygen saturation ($P > 0.05$). No significant change in heart rate or mean arterial pressure was found in either group (Table 2). There was no significant difference between groups in biochemical parameters or temperature ($P > 0.05$).

Sedation

Magnesium sulphate infusion, when added to sufentanil infusion, decreased the consumption of sufentanil at all times except during the first hour ($P < 0.001$; Fig. 1). There was no significant difference between the groups in terms of BIS values ($P > 0.05$; Fig. 2).

Table 1

Clinical characteristics of the patients included

Characteristic	Group 1 (n = 15)	Group 2 (n = 15)
Age (years)	48.2 ± 6.4	51.1 ± 5.3
Weight (kg)	62.3 ± 8.55	64.5 ± 7.8
APACHE II score	12.3 ± 4.3	13.4 ± 4.6
Death (*n*)	4	4
Aetiology (*n*)		
Medical	4	5
General surgical	6	4
Trauma	5	6

There were no significant differences between groups. Group 1 received sufentanil infusion alone, whereas group 2 received sufentanil plus magnesium sulphate. Unless otherwise stated, values are expressed as means ± standard deviation. APACHE, Acute Physiology and Chronic Health Evaluation.

Outcome

The overall hospital mortality rate was similar in both groups (26.6%). All of those who died did so while being mechanically ventilated. Mean survival time was 7 ± 3 days in the group receiving sufentanil plus magnesium sulphate and 7 ± 4 days in the group receiving sufentanil alone. The duration of mechanical ventilation and the number of ventilator free days (calculated as the number of days a patient was alive and without mechanical ventilation at 28 days) were similar between the groups. In the sufentanil and sufentanil plus magnesium groups, ventilation duration was 6 ± 2 and 7 ± 3 days and number of ventilator free days was 9 ± 3 and 8 ± 4 days, respectively ($P > 0.05$).

Side effects

No side effects were noted during or after administration of sufentanil infusion and sufentanil plus magnesium infusion.

Discussion

Sedatives are common adjuncts in the treatment of anxiety and agitation. The causes of anxiety in critically ill patients are multifactorial and probably secondary to the continuous noise (making it impossible to communicate), continuous ambient lighting and excessive stimulation (inadequate analgesia, frequent vital sign monitoring, repositioning, lack of mobility and room temperature) that are characteristic of the ICU setting. Efforts to reduce anxiety, including frequent reorientation, maintenance of patient comfort, provision of adequate analgesia and optimization of the environment, may be supplemented with sedatives [1,2].

The BIS of the electroencephalogram is an empirical, statistically derived variable that provides information about the interaction of brain cortical and subcortical regions. Sigl and

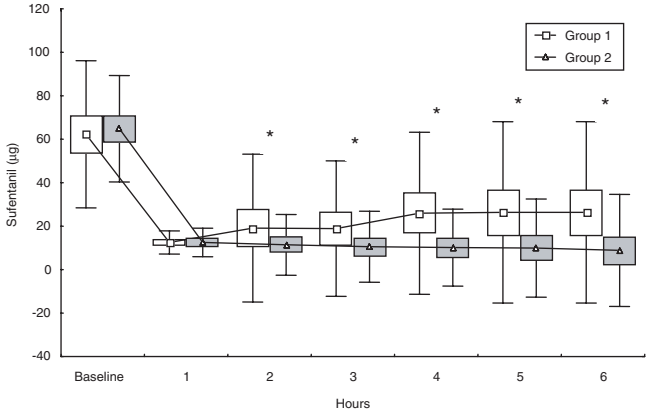
Table 2

Hemodynamic parameters, and calcium and magnesium levels

		Period after sedative infusion				
Parameter/level	Baseline	Immediately after	2 hours	4 hours	6 hours	24 hours
Heart rate (beats/min)						
Group 1	90 ± 12	89 ± 11	88 ± 12	90 ± 13	92 ± 11	91 ± 13
Group 2	88 ± 11	91 ± 9	89 ± 11	88 ± 12	90 ± 12	88 ± 12
Mean arterial pressure (mmHg)						
Group 1	74.1 ± 9.2	73.5 ± 14	76.3 ± 9.5	77 ± 12.5	75 ± 12.5	75 ± 8.5
Group 2	75.2 ± 8.8	74 ± 10.7	76.4 ± 12.0	74 ± 14.8	74 ± 14.8	73 ± 9.8
Calcium (8.9–10.3 mg/dl)						
Group 1	9.2 ± 1.1	9.1 ± 1.2				9.0 ± 1.3
Group 2	9.1 ± 1.3	8.9 ± 1.1				8.9 ± 1.2
Magnesium (1.8–3.5 mg/dl)						
Group 1	3.06 ± 0.83	3.07 ± 0.79				3.08 ± 0.68
Group 2	2.97 ± 0.95	4.0 ± 1.31				3.1 ± 0.73

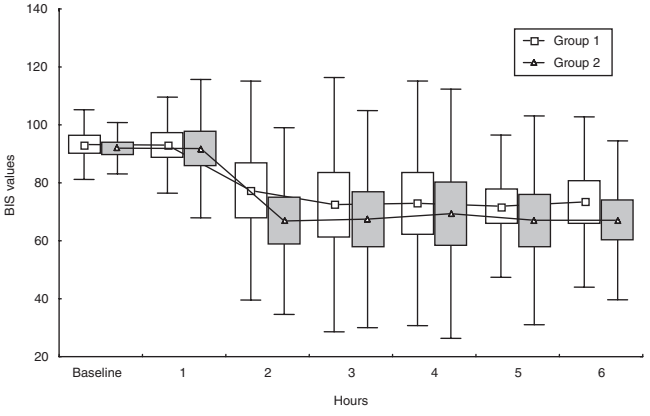
There were no statistically significant differences between groups ($P > 0.05$). Group 1 ($n = 15$) received sufentanil infusion alone, whereas group 2 ($n = 15$) received sufentanil plus magnesium sulphate. Values are expressed as means ± standard deviation.

Figure 1



Hourly consumption of sufentanil. Group 1 ($n = 15$) received sufentanil infusion alone, whereas group 2 ($n = 15$) received sufentanil plus magnesium sulphate. Data are expressed as means ± standard deviation. *$P < 0.001$, group 1 versus group 2.

Figure 2



Hourly bispectral index (BIS) values. No statistically significant differences were found between the groups ($P > 0.05$). Group 1 ($n = 15$) received sufentanil infusion alone, whereas group 2 ($n = 15$) received sufentanil plus magnesium sulphate. Data are expressed as means ± standard deviation.

Chamoun [13] reported technical details and rationale for the use of BIS. First, BIS provides information regarding interaction between cortical and subcortical areas, which changes with increasing amounts of hypnotic drugs. Second, the BIS is an empirical, statistically derived measurement that was developed by analyzing a large database of electroencephalograms from individuals who had received hypnotic agents. Third, the BIS measures a state of the brain and not the concentration of a particuler drug. Fourth, interpretation of the BIS is based on the assumption that sedation is intended to produce a state of sleep that includes a lack of awareness and a lack of recall, whereas analgesia is intended to produce a state of reduced pain perception manifested by decreased autonomic responses to noxious stimuli. Finally, in general a BIS score of 100 reflects the awake state, 80 reflects some sedation, 60 reflects a moderate level of hypnosis, and 40 reflects a deep hypnotic state [14]. In the present study BIS values were maintained in the range 61–88.

BIS is a processed electroencephalographic measurement that correlates with the sedative properties of single anaesthetic agents. Use of combinations of hypnotics and opiates to achieve sedation has become common. BIS is useful in the ICU for monitoring sedation (and preventing over-sedation) and for shortening the duration of ICU stay, and a consequent decrease in hospital costs associated with its use may be anticipated [15]. However, several questions have been raised regarding the use of BIS in the ICU concerning the widespread use of opioids (which reduces the validity of BIS) [15,16], interpretation difficulties in neurological diseases [17] and controversial studies that demonstrated decreased correlation between clinical sedation scores and BIS [17–19]. For example, a study conducted in a paediatric ICU [20] demonstrated that opioids do provide some degree of sedation.

Kroll and List [21] found analgesia and sedation with sufentanil to be satisfactory in critically ill patients. At a dosage range of 0.75–1.0 μg/kg per hour, this drug can safely be given to patients undergoing controlled mechanical ventilation. Wappler and coworkers [22] found that continuous infusion of sufentanil (1 μg/kg per hour was given initially) for analgesia and sedation is suitable for intensive care patients with a short stay in the ICU. Prause and colleagues [10] found that critically ill patients under continuous sedation with sufentanil (median 0.44 μg/kg per hour) exhibit a statistically significant rise in arterial carbon dioxide tension, but this respiratory depression is only slight and has no clinical significance. Mechanically assisted spontaneous ventilation modes can safely be used under continuous sedation with sufentanil. In the present study all patients initially received 1 μg/kg sufentanil by intravenous bolus.

There is a suggested role for magnesium in almost every physiological system. Key underlying mechanisms of action are those of calcium antogonism via calcium channels, regulation of energy transfer, and membrane sealing or stabilization [23,24]. This has led to several studies on the central and peripheral nervous systems, and the cardiovascular, respiratory, endocrine and reproductive systems. Magnesium's action as an anticonvulsant is secondary to antagonism at *N*-methyl-D-aspartate receptors [25]. Stimulation of this subgroup of glutamate receptors is known to lead to excitatory postsynaptic potentials, causing seizures. Magnesium has successfully been used as an anticonvulsant in eclampsia [26].

In addition, magnesium is known to have a marked antiadrenergic effect. This is mediated by a variety of mechanisms, of which the most important is probably calcium channel blockade. Calcium plays a fundamental role in stimulus–response coupling of catecholamine release from the adrenal medulla and adrenergic nerve terminals, and its role in adrenal catecholamine release is well described [11]. In tetanus, magnesium has been used to treat both muscle spasm and autonomic dysfunction, which leads to large increases in catecholamine release [27].

Calcium channel blockers have antinociceptive effects in animals and potentiate the analgesic effects of morphine in patients with chronic pain [28,29]. As mentioned above, magnesium is also an antagonist of *N*-methyl-D-aspartate receptor ion channels, and this may explain part of its analgesic activity [30]. The analgesic effect of magnesium has been demonstrated both in human and in animal studies. Its effect on decreasing perioperative analgesic [31] and anaesthetic [32] requirements was demonstrated in various studies. In the present study, under highlights of magnesium's effects, when used for sedation/analgesia in ICU, we aimed to investigate the influence on sufentanil dose. Attygalle and Rodrigo [27] administered 2–3 g/hour magnesium in tetanus. In the present study we used a similiar dose of 2 g/hour magnesium.

Magnesium is utilized in the control of spasms in eclampsia and the safety of the therapeutic range (2–4 mmol/l) is well established, because areflexia only occurs at levels above 4 mmol/l and muscle paralysis above 6 mmol/l [27]. Magnesium does not cause sedation at serum concentrations below 8 mmol/l as long as ventilation is adequate (because it does not easily cross the blood–brain barrier) [27]. Attygalle and Rodrigo [27] administered 2–3 g/hour magnesium in tetanus. Those investigators found that magnesium sulphate can be used as the sole agent for the control of spasms in tetanus without the need for sedation and artificial ventilation. In our study serum magnesium concentrations did not increase to above 5 mmol/l but these concentrations increased the effectiveness of sufentanil when the agents were administered together.

However, the patients studied here were not postoperative patients and were not extubated at the end of the study; we were therefore unable to evaluate the effect of infusion of sufentanil plus magnesium on extubation criteria. We aimed to determine the effect of sufentanil plus magnesium infusion over a short period of time. Further studies in postoperative patients are needed to determine effects of sufentanil plus magnesium infusion on extubation criteria.

This is the first clinical study to demonstrate that magnesium infusion decreases sufentanil requirements. Because of the limited number of patients included and the short period of observation, our findings must be confirmed by larger clinical trials of magnesium infusion titrated to achieve prespecified levels of sedation. Furthermore, randomized clinical studies are needed to determine the effects of magnesium infusion on opioids.

Key messages

- We assessed whether the addition of magnesium infusion in ICU patients decreased the sufentanil requirements using bispectral index
- This clinical study demonstrated that magnesium infusion decreased sufentanil requirements

Competing interests

None declared.

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