Metabolic and endocrine effects of sedative agents

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Purpose of review

To bring to the attention of the clinician the metabolic effects of most common sedatives and analgesics used in critically ill patients.

Recent findings

Most patients admitted to the intensive care unit require sedation and analgesia to reduce anxiety, agitation, and delirium and provide pain relief. Inappropriate sedation and analgesia techniques can cause harm to the already compromised patient if they do not take into account the metabolic effect they produce.

Summary

Metabolically critical illness can be divided in two phases, and acute and a prolonged one. Whereas the acute or hypermetabolic phase is characterized by elevated circulating concentration of catabolic hormones and substrate utilization to provide energy to vital organs, the prolonged or catabolic phase of critical illness is marked by reduced endocrine stimulation and severe loss of body cell mass. The most common analgesic and sedative agents used in the intensive care unit, if used in small or moderate doses, do not interfere significantly with the metabolic milieu; however, prolonged infusions, and in high doses, without adequate monitoring of level of sedation and quality of analgesia, can precipitate morbid events. Further research is needed in the metabolic aspects of analgesia and sedation in the intensive care unit, particularly if a multimodal pharmacologic strategy is used whereby multiple interventions aim at minimizing the risk of overdosing and contributing to attenuation of the stress response associated with critical illness.

Keywords

hormones, metabolism, sedative and analgesic drugs, stress response

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Abbreviations

ACTH	adrenocorticotropic hormone
APACHE-II	Acute Physiology and Chronic Health Evaluation II
GABA	γ-amino butyric acid
ICU	intensive care unit
IGF	insulinlike growth factor

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Introduction

Injury initiates a series of physiologic responses, the magnitude of which depends on the intensity of the stressor. The defense mechanisms are also related to the nature of the injury and are activated during the initial period. If the noxious stimulus persists, exhausting mechanisms are initiated, leading to progressive tissue catabolism and subsequently to death [1]. The rational use of sedatives and analgesics can attenuate some of the most detrimental responses and facilitate the recovery process.

Metabolic and endocrine events in critical illness

During the first hours and days of critical illness, the demand for energy by the vital organs such as the brain and the immune system is elevated. The circulating concentrations of catecholamines, growth hormone, glucagon, and cortisol are raised, whereas insulin level is depressed. These hormones are responsible for activating hepatic glycogenolysis and gluconeogenesis. The circulating concentration of glucose is increased, reflecting a state of insulin resistance and incapacity by the cell to oxidize glucose. Once hepatic glycogen is exhausted, gluconeogenesis is initiated with the intent to supply glucose for those organs that depend entirely on glucose as energy substrate. Gluconeogenic materials include amino acids made available from the increased protein breakdown and glycerol from lipolysis, whereas free fatty acids contribute to increasing hypertriglyceridemia [2].

From a metabolic point of view, is possible to distinguish two different phases of critical illness, an acute and a prolonged one. Throughout evolution, the human species has been selected to survive disease and trauma; the acute metabolic response is thought to be at least partially evoked by endocrine changes, including not only an activated hypothalamic-pituitary-adrenocortical axis but also hypersecretion of prolactin and growth hormone in the presence of low circulating insulinlike growth factor I (IGF-I) and a low-activity state of the thyroid and gonadal axis. It is still unclear to what extent some of these defense mechanisms may provide an exaggerated response and, as a consequence, be harmful.

The development of intensive care medicine, with its nutritional and vital organ function support, has enabled humans to survive conditions that before were lethal. Highly technologic interventions in the natural course of the dying process have unmasked previously unknown conditions, including a nonspecific wasting syndrome: despite feeding, protein continues to be lost from vital organs

and tissues due to both activated degradation and suppressed synthesis, whereas reesterification (instead of oxidation) of free fatty acids allows fat stores to build up. Moreover, hyperglycemia and insulin resistance, hypoproteinemia, hypercalcemia, intracellular water and potassium depletion, and hypertriglyceridemia accompany the wasting, which often prompt symptomatic treatment [1].

Human data on the neuroendocrine characteristics of prolonged critical illness (>10 days) are now becoming available, and they appear to be quite different from those observed in the acute phase. Whether they also represent a beneficial adaptation or, instead, a neuroendocrine dysfunction or exhaustion is not been established. It appears that whereas the acute phase is characterized mainly by an actively secreting anterior pituitary gland and a peripheral inactivation or inactivity of anabolic hormones, prolonged critical illness is marked by reduced neuroendocrine stimulation.

Insulin

The IGF binding protein number 1 (IGFBP-1) is an important regulating mediator of the IGF bioavailability, and its correlation with mortality has been demonstrated in critical care patients, in whom IGF-I, IGF-II, IGFBP-1, IGFBP-2, IGFBP-3, and IGFBP-3 protease levels are altered [3]. In the liver, IGFBP-1 is transcriptionally suppressed by insulin, and it is a specific marker of hepatic insulin sensitivity. In patients with intensive care unit (ICU) length of stay longer than 7 days, intensive treatment with hexogen insulin (80–110 mg/dL *vs* 180–210 mg/dL) determined a lowering of glycemia, but without effect on serum IGFBP-1, whereas values were significantly higher in patients who would die. The predictive value of serum IGFBP-1 is in fact similar to the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score [4].

Cortisol

In critically ill patients, circulating levels of cortisol are increased from two to 10 times during the first 24–48 hours of ICU stay; particularly, cortisolemia levels greater than 600 n*M* are related to a lower probability of survival [5]. During the prolonged phase of critical illness, conversely, cortisol decreases, until it often becomes inadequate, even if the hypothalamic-pituitary-adrenocortical axis functions well [6]. The stimulating test with adrenocorticotropic hormone (ACTH) can identify patients with hypocortisolemia, in whom steroid therapy could have a beneficial effect [7].

Thyroid hormones

The total serum concentrations of tiroxin and triiodothyronine are globally decreased in critically ill patients, likely due to the reduction of thyrotropin, which dramatically loses its pulsatile release; the nadir is reached on average at the 4th ICU day. The altered feedback between thyrotropin-releasing hormone and thyrotropin, 'sick euthyroid syndrome', is associated with lethargy, ileus, pleural and pericardial effusions, glucose intolerance and insulin resistance, hypertriglyceridemia, and decreasing muscular protein synthesis [1]. These effects contribute to perpetuation of protein catabolism. The serum levels of tri-iodothyronine and thyroxine in high-risk patients are correlated with survival [5].

Growth hormone

The beneficial effects of exogenous growth hormone (from five to 20 times the normal hematic level) could attenuate the catabolic response, improving the protein turnover and the nitrogen balance in burns, postsurgical, septic, and critical patients [8]. In a large randomized controlled trial performed in Finland and northern Europe in 1999, however, treatment with large doses of growth hormone increased mortality and morbidity in adult critical patients [9]. The explanation of this result is not clear yet: growth hormone causes insulin resistance and contributes to hyperglycemia and, moreover, prevents glutamine mobilization from the muscle, making it less available for the fast turnover cells such as leukocytes and enterocytes and for the hepatic production of glutathione. Finally, the increase of multiple organ failure, septic shock and unrestrained infections in the treated group, leads us to think growth hormone can worsen the immune response, changing the reactive oxygen species and proinflammatory cytokines' formation.

Catecholamines

The acute phase of all critical illnesses is characterized by major catecholaminergic activation. Above all, the excessive hormonal, metabolic, and inflammatory response leads to increased oxygen consumption, hemodynamic instability, intravascular fluids shifting, thermic increase, and altered coagulation. It has already been demonstrated that the use of most analgesic and sedative agents (fentanyl, morphine, midazolam, propofol, clonidine) can contribute to a decrease in hemodynamic complications [10], modulating the serum and urine concentrations of endogenous catecholamines, cortisol, and dopamine.

Melatonin

Sleep disturbances are common in ICU patients, and benzodiazepines, opioids, and clonidine are responsible for a decrease in the rapid eye movement phase and in slow wave sleep [11]. Moreover, mechanical ventilation, such as with benzodiazepines and clonidine, abolishes the circadian rhythm of melatonin secretion [12•], whereas morphine can stimulate melatonin release [13]. Delirium, hallucinations, anxiety, and depression can also alter the circadian rhythm of melatonin [14]. It is not known whether treatment with melatonin could decrease the severity of sleep disturbances and hence inhibit the development of ICU delirium.

Metabolic effects of pain

Acute experimental pain, without surgical intervention, has been shown to activate in volunteers several changes in hormone levels and metabolic pathways (insulin resistance, increased plasma cortisol, catecholamines, growth hormone and glucagon, and hyperglycemia) [15] and low oxygen tension [16]. This indicates that pain, even without inflammation, can elicit a lasting endocrine and metabolic response of sufficient magnitude. Critically ill patients are exposed to several stimuli of different intensity, some of them very painful, like bronchoaspiration or tracheal extubation, which can reach (on a Visual Analogue Scale [17] from 0–10 cm) 4.9 and 6.6 cm respectively [18]. The realization that continuous acute painful stimuli, superimposed on the nature of injury, can enhance its physiologic and metabolic response has prompted clinicians to attenuate this response by introducing pharmacologic interventions.

Metabolic and endocrine effects of analgesics and sedatives

Although the subject of analgesia and sedation has been widely discussed in the critical care literature, little is known about the metabolic effect of analgesics and sedatives used in the ICU. In addition, the potential physiologic repercussion these pharmacologic agents might have on organ function and the healing process of critically ill patients has not received adequate attention. This might be due to the difficulty in dissecting the separate effects of these agents when in the presence of more powerful triggers such as inflammation, malnutrition, and immobilization. Inappropriate sedation techniques that do not take into account the possible impact on metabolic and immune function of the critically ill patient can cause morbidity and even mortality, as occurred with the use of long-term infusion of the imidazole agent etomidate in the early 1980s, and recently with large doses of propofol infusion. In this section, an attempt is made to gather all the published information on the hormonal and metabolic effects of analgesics and sedatives used in the ICU. Inhibition or stimulation may become important clinically when the sedative or analgesic is administered for a long period of time, especially if changes in circulating inflammatory mediators have already been impaired, e.g., the adrenocortical response. The impact of sedation and analgesia on some aspects of the inflammatory response is not discussed here.

Opioids

Opioids are largely used in the ICU: they offer optimal pain control acting mainly on gamma and kappa receptors, and through their analgesic effect, they attenuate the metabolic effects associated with injury. In recent clinical guidelines, morphine, fentanyl, and hydromorphone have been recommended [19]. Morphine, a water-soluble compound, is commonly used in the ICU. It causes vasodilatation, a decrease in heart rate, as a result of its sympatholytic action. Administered at high doses during cardiopulmonary bypass grafting, morphine has been shown to inhibit circulating concentration of catecholamines, cortisol, and growth hormone. At the current moderate doses used in the ICU, however, morphine has a minimal effect on cortisol and no effect on plasma concentration of epinephrine [20].

Fentanyl and hydromorphone are acceptable alternatives to morphine, with the characteristics of being synthetic and devoid of histamine release properties. They are more potent and cause fewer hemodynamic changes than morphine, even when used in large doses. Remifentanil, an ultrashort-acting opioid, is often used in the ICU, particularly in neurocritical care, to attenuate the hemodynamic response to painful stimuli of physiotherapy, bronchial aspiration, and radiologic interventions. Remifentanil is a potent opioid that causes hypotension and vasodilatation, probably due to inhibition of noradrenaline. The administration of opioids is associated with side effects such as nausea and vomiting, itching, and ileus. Opioids have been shown to affect the immune response and this might be undesirable in critically ill patients who are already compromised and at risk of acquiring opportunistic infections.

Benzodiazepines

Benzodiazepines are the most commonly used medications for inducing sedation and treating agitation in the ICU. These drugs promote anxiolysis, hypnosis, anticonvulsive activity, amnesia, and skeletal muscle relaxation. They act by potentiating γ-amino butyric acid (GABA) receptor complex-mediated inhibition of the central nervous system. Midazolam, because of its enhanced lipophylic characteristics, has a rapid onset of action with limited effects on cardiorespiratory depression. Use of diazepam or midazolam, together with fentanyl, maintains fairly low endogenous levels of epinephrine and norepinephrine. Continuous infusion of midazolam does not inhibit adrenocortical axis activity: cortisol secretion, studied by an ACTH infusion test, was not inhibited [21], and plasma catecholamine production was reduced, although not significantly, in postoperative ventilated patients requiring intensive therapy, when compared with bolus of diazepam or sedation with isoflurane [22]. Benzodiazepines have been shown to enhance the analgesic effects of morphine, and this synergism may decrease the doses of benzodiazepines needed to achieve adequate sedation. Because of the potential disadvantages of continuous sedation, attempts have been made to interrupt infusion of sedatives in critically ill patients requiring mechanical ventilation, without major metabolic side effects. The use of flumazenil, the specific pharmacologic antagonist of benzodiazepines, in patients receiving continuous sedation with midazolam is associated with increased circulating levels of epinephrine and norepinephrine. This rapid increase in plasma catecholamines is then followed by a return to normal range within the next 2 hours; in contrast the cortisol levels remain unchanged.

Transitory awakenings obtained with flumazenil do not involve a stress response, whereas the increase in plasma catecholamines suggests sympathetic nervous system activity [23]. High doses of diazepam are associated with the development of metabolic acidosis resulting from the propylene glycol component of the carrier solution [24]. Similarly, large doses of lorazepam have been shown to cause polyethylene glycol nephrotoxicity [25].

Another important aspect of benzodiazepine and opioid long-term infusion is the withdrawal acute syndrome [26]; common symptoms include seizures, tremor, confusion, anxiety, insomnia, vomiting, tachycardia, and fever [27]. These symptoms are more severe after cessation of short-acting rather than long-acting benzodiazepines [28], and for this reason, when large doses of midazolam have been administered over long periods, the clinician should use a tapering regimen of intravenous midazolam over several days. Alternatively, a transition to long-acting benzodiazepines may be of benefit.

Propofol

Propofol has been used for ICU sedation since the late 1980s and has gained popularity for its rapid onset and offset. As with benzodiazepines, propofol activates the GABA receptors to produce central nervous system depression. Propofol is cleared faster than midazolam and is rapidly eliminated from the central compartment. Recovery times and blood propofol concentrations were found to be similar after 24, 48, 72, and 96 hours of drug infusion [29] with a measurable blood concentration; for these characteristics it is possible to modulate a more rapid weaning by mechanical ventilation [30,31] and therefore a more rapid natural endocrine/metabolic restoration. Following cardiopulmonary bypass surgery, continuous infusion of propofol in the ICU for the first postoperative 12 hours has been shown to obtund the rise of plasma cortisol (−31%) and epinephrine (−53%), urinary cortisol (−59%), dopamine (−38%), epinephrine (−45%), and norepinephrine (−48%) [10]. These findings indicate that intravenous propofol infusion after cardiac surgery provides a stable hemodynamics, a decrease in oxygen consumption, and fewer postoperative cardiocirculatory complications. Propofol infusion has been shown to have no significant effects on adrenal steroidogenesis in critically ill patients [32]. Propofol administration has been associated with arterial hypotension, and this is more evident with bolus injection than with continuous infusion. The mechanism of hypotension is peripheral vasodilatation, probably mediated by inhibition of noradrenaline. No changes in heart rate have been reported. The fall in cardiac output can also be the result of myocardial depression. Supplementary intravenous administration of fluid and vasopressors can be used to correct the change in hemodynamics. Propofol is supplied in a lipidic emulsion, and if it is infused at high doses it could lead to hypertriglyceridemia [33]. A randomised, multicenter study has not been able to demonstrate a significant risk of hypertriglyceridemia, whether 1% or 2% propofol solutions are used [34]. It is likely that the risk will be decreased with the recently introduced propofol 2% solution [35].

Propofol infusion syndrome

Propofol infusion syndrome is a rare and often fatal syndrome originally described in critically ill children and lately reported in adults undergoing long-term (>48 hours) propofol infusions at high doses (>4 mg/kg/h). The main features of the syndrome are cardiac failure, rhabdomyolysis, severe metabolic acidosis, and renal failure [36]. The syndrome has been reported mostly in patients with acute neurologic illnesses or acute inflammatory diseases complicated by severe infections or sepsis and receiving catecholamines or steroids in addition to propofol. It is hypothesized that central nervous system activation with production of catecholamines and glucocorticoids, and systemic inflammation with cytokine production, are priming factors for cardiac and peripheral muscle dysfunction [37]. There is evidence that, at the subcellular level, propofol impairs free fatty acid utilization and mitochondrial activity with a rise in malonylcarnitine, which inhibits the transport protein for long-chain fatty acids (carnitine palmityl transferase 1). Imbalance therefore exists between energy demand and use ('mitochondrial respiratory-chain enzyme deficiency'): this results in a decrease in ventricular performance and cardiac contractility [38]. This might explain the lack of response to catecholamines and the need for increasing inotropic support in these patients. Rhabdomyolysis can be explained by direct myocytolytic effect of catecholamines, resulting in myofibrillar degeneration. In light of several reports of propofol infusion syndrome, prolonged high-dose propofol infusions (>80–100 μg/kg/min for 48–72 hours) should be administered with caution [39]. Monitoring for early signs of this syndrome (myoglobin and creatine kinase levels) and the need for increasing inotropic support have been proposed [40]. Administration of pentobarbital may be considered alternatively, although the potent cardiac depressant effects of this long-acting barbiturate should be considered.

α-2 Agonists

Dexmedetomidine is a selective α-2 agonist approved for intensive care sedation in patients receiving mechanical ventilation. It has both analgesic and anxiolytic properties. It is an imidazole compound with potential inhibitory effects, similar to etomidate, on cortisol synthesis. The latter has been demonstrated in in-vitro and in-vivo animal studies. In a recent study in which the endocrine and inflammatory responses in patients needing postoperative short-term sedation in the ICU were assessed, however, the infusion of dexmedetomidine did not inhibit adrenal steroidogenesis [41]. This was accompanied by elevated circulating concentrations of growth hormone and low insulin and catecholamines. In addition, analgesic

opioid need was decreased with stable hemodynamics [42]. α-2 agonists stimulate growth hormone secretion without altering glycemic control, whereas C-peptide (related to endogenous secretion of insulin) is decreased [43]. This effect could be related either to the direct action of these drugs on pancreatic islands, to better peripheral glycemic control with consequent decreased insulin secretion, or to catecholamine suppression.

At present there are no data on the use of dexmedetomidine for long-term sedation in the ICU. The pharmacologic profile of α-2 agonists could make these drugs more suitable for the ICU setting than some of the traditional ones, in the sense that they can provide minimal sedation with excellent analgesia, together with some attenuation of metabolic stress response and myocardial protection. It remains to be seen whether α-2 agonists can be safely used during prolonged critical illness when the quality and intensity of sedation and analgesia become critical for the patient's survival.

Ketamine

Ketamine is a phencyclidine derivative causing a dissociative state. It provides excellent analgesia and amnesia, with minimal respiratory depression. It activates the sympathetic nervous system resulting in an increase in heart rate, cardiac output, and blood pressure. It is rarely used in the ICU because of the hallucinations and emergence delirium with which it is associated. There are some clinical conditions, however, such as status asthmaticus, in which ketamine is highly indicated for its properties as a bronchodilator.

Etomidate

In the early 1980s, etomidate infusion in critically ill patients was found to be associated with an unusual increase in mortality [44]. Whereas etomidate given to relatively fit patients causes a reversible adrenocortical suppression, in critically ill patients the impaired adrenocortical synthesis of cortisol leads to multiorgan failure and death. A single dose of etomidate is used for induction of anesthesia when cardiovascular stability is needed, with no ill effects. Recent studies have also shown that administration of single-dose etomidate in critically ill patients does not interfere with cortisol synthesis for a certain period, although a small rise in cortisol has been reported after ACTH stimulation, implying that there is some residual effect on the ability of the adrenal cortex to respond to ACTH 24 hours after a single dose [45].

Multimodal intervention: time for consideration

It is clear from the several reports on the subject that sedation and analgesia of the critically ill patients represent a challenge for the busy clinician confronted with multiple organ failure and a limited pharmacologic armamentarium. It appears that unimodal interventions such as propofol or benzodiazepines have limitations and can compromise body functions as a result of overdosing. A more global approach based on multimodal interventions would make more sense when considering that the pathophysiology of injury is comprised of a constellation of insults beyond those already known (e.g., sleep disorders, hypoxia, immobilization, malnutrition, autonomic imbalance), and therefore one drug alone cannot accomplish what is required. It is therefore necessary to consider a different approach and use of other medications and interventions that can be safely introduced (of course, taking specific precautions with the type of patient to be treated), such as epidural local anesthetics, nonsteroidal anti-inflammatory drugs, acetaminophen, steroids, gabapentin, and melatonin. The possible advantage of using a multimodal approach is to decrease the risks associated with unimodality and to attenuate different stressors involved in the injury process. For example, the use of thoracic epidural analgesia, achieved with a mixture of local anesthetics and opioids, in the traumatized patient with chest, abdomen, or lower limb fractures, would provide optimal analgesia, attenuate some of the stress response associated with the injury, decrease the hyperglycemia of trauma, facilitate lung ventilation and oxygenation, and restore bowel function. This therapeutic modality could therefore be part of the multimodal intervention aiming at treating several aspects of the pathophysiology beyond analgesia and sedation.

Conclusion

Some of the clinical manifestations occurring as a result of critical illness can be attenuated by sedatives and analgesics, although the latter can be responsible, if not used adequately, for causing harm to the already compromised patient. Further research into multimodal intervention is needed so that various aspects of critical illness can be appropriately targeted and treated.

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