Sedation and Analgesia in the Intensive Care Unit

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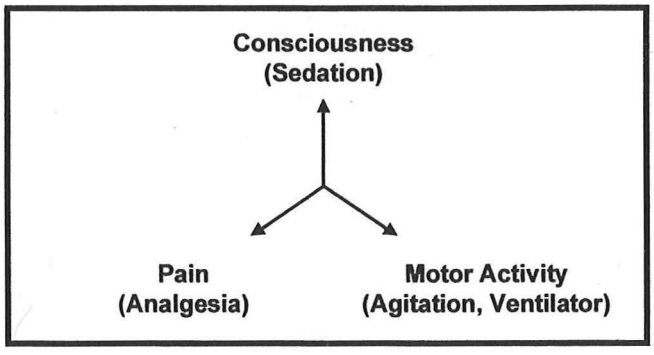

Now blessings light on him that first invented this same sleep! It covers a man all over, thoughts and all, like a cloak.
~ Miguel de Cervantes, *Don Quixote de la Mancha*

Sleep's the only medicine that gives ease.
~ Sophocles, *Philoctetes*

Sleep is a reward for some, a punishment for others.
~ Isidore Ducasse, *Poésies*

To sleep: perchance to dream: aye, there's the rub; for in that sleep of death what dreams may come.
~ William Shakespeare, *Hamlet*

Moderation in all things.
~ Terence, *Andria (The Lady of Andros)*

This is to acknowledge that W. Douglas Pitcher, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Pitcher will not be discussing "off-label uses in his presentation.

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Anxiety, pain, disorientation, sleep deprivation, loss of personal autonomy and modesty can produce a veritable nightmare for critically-ill patients (1-4). Fortunately for most, the nature of our response to severe illness and/or the amnestic properties of drugs used for sedation often leave the patient with little recollection of their time in the ICU (5-10). However, in some cases, confusion and delirium can cause even routine aspects of care to be misinterpreted by the patient, even leading to accusations of abuse (11-15).

Further, these unpleasant experiences may produce behavior which can itself be life-threatening. Newer modes of mechanical ventilation and the use of invasive monitoring have brought with them the need for deeper levels of sedation.

Thus, an important part of caring for these patients focuses on providing relief, a process loosely referred to as sedation. Sedation is actually a complex process, but in general should be thought of as involving management of three related problems: the level of consciousness or sleep/wakefulness (sedation), pain (analgesia), and overt motor behavior (agitation, ventilator co-ordination).

The first step in regulating these is to identify the causes of agitation, correcting the primary problem whenever possible rather than reflexively resorting to pharmacologic intervention. Some of the many causes of what we see as an agitated patient are listed below.

Causes of Agitation

Anxiety, fear	Hypoglycemia
Lack of orientation/reassurance	Hyperosmolarity
Patient positioning	Hepatic, uremic encephalopathy
Untreated pain	Sepsis
Inappropriate ventilator settings	Primary CNS event
ICU psychosis	Withdrawal syndromes
Hypoxia, hypercarbia	Drug toxicity
Electrolyte disorders (Na^+, Ca^{++})	Steroid psychosis

Commonly, however, treatment with sedation/analgesia agents is necessary and is used in most patients requiring mechanical ventilation (16-18). Sedation/analgesia can provide a range of potential benefits including relief of anxiety, pain, delirium, and sleep deprivation. The patient may require control of agitation and restraint to facilitate co-ordination with mechanical ventilation, and to prevent loss of the endotracheal tube, intravenous lines, and invasive monitoring devices. Sufficient sedation may minimize or eliminate the need for neuromuscular blockade. Ventilation may be aided by improved respiratory compliance or by reducing oxygen consumption, CO_2 production, and thus minute volume requirements. In some cases, sedative agents may be neuroprotective, reduce cerebral metabolic activity, or reduce intracranial pressure.

These benefits do not come cheaply, however. Hypotension and bradycardia can occur with certain agents, especially with rapid bolus infusion. Prolonged sedation is particularly problematic (see below) and often leads to excessive duration of mechanical ventilation and prolonged length of stay (19). These agents interfere with our ability to assess neurologic function. Heavily sedated patients are unable to interact with family or participate in treatment decisions. Continuous infusions, especially with multiple agents, are a common cause of excessive fluid administration (20). Infectious complications are associated with sedation; use of sedation is a risk factor for nosocomial pneumonia (21). These agents may be abused when used excessively for "chemical restraint" and overuse has been correlated with nursing understaffing (22,23). Withdrawal syndromes have been described (24,25).

When patients fail to regain consciousness promptly, physicians find themselves using otherwise unnecessary diagnostic studies such as head CT, MRI, or lumbar puncture; this not only increases cost, but exposes the patient to the risks of intra-hospital transport (26,27). The drugs themselves can be expensive (see below) and may increase indirect costs when complications arise. Certain agents may also have interesting unintended effects such as suppression of adrenocoritcal function, alteration of immune function, hyperlipidemia, pancreatitis, and seizures; these effects will be discussed in greater detail below.

While there are a host of agents available for sedation and analgesia, this review will focus on the more commonly used agents: lorazepam, midazolam, and propofol (used for sedation); morphine and fentanyl (analgesics); and haldoperidol (control of agitation). It is not my intent to comprehensively review each of these agents; there are numerous review articles available for this purpose (28-39). In addition, multiple studies dealing with efficacy, safety, pharmacokinetics, and pharmocodynamics are included in the bibliography (40-72) along with a number of comparative trials (20,73-85).

Lorazepam (Ativan) is a benzodiazepine which is the longest acting (hours to days) of the drugs described here. It has a slow onset with peak effect at 30 to 40 minutes; this is important to keep in mind as repeated dosing during titration without allowing time for maximal effect may lead to over-sedation, accumulation, and prolonged effect. It is usually used by intermittent i.v. bolus (1-2 mg q 2-4 hours) but is also used as a continuous infusion (0.01-0.06 mg/kg/hr).

Lorazepam is difficult to maintain in solution and may precipitate in i.v. tubing and bags if one attempts to over-concentrate the drug (20,73,86). Solubility is best in D5W and there is twice as much delivery solvent per ml in the 2 mg/ml formulation as compared to the 4 mg/ml preparation. The drug tends to be lost from solution over time due to adsorption, especially to PVC materials (87). For these reasons, lorazepam mixtures should be made from the 2 mg/ml preparation in D5W, preferably using glass containers, at concentrations not to exceed 0.2 mg/ml. Drug mixtures should be made and changed q 12 hr. These

problems may be a source of what may appear to be excessive dose requirements in some patients (i.e. the patient is not really receiving what you think you are delivering) and also adds to pharmacy time and indirect drug costs. The delivery vehicle contains propylene glycol and cases of intoxication have been reported.

Lorazepam has little cardiovascular effect. It also has no active metabolites and thus may be desirable for patients with liver failure. Lorazepam is often used as first-line therapy for patients with minimal sedation requirements.

Midazolam (Versed) is a short-acting benzodiazepine (1-2 hours) which has rapid onset (2-5 minutes). Because of its relatively short duration of action, it is usually given as a continuous infusion (0.01-0.25 mg/kg/hr). During titration, a small bolus (1-2 mg) should be given before increasing the infusion rate. Although it is generally thought of as being short-acting, prolonged sedation after discontinuation is not uncommon (see below). The drug is metabolized by the liver and its metabolites are themselves active sedatives. Elimination is via the kidneys. Thus, caution must be exercised in patients with liver or renal impairment. As with other benzodiazepines, midazolam has significant amnestic properties, but it has no analgesic effect (see below). The drug is one of the most commonly used agents for sedation in patients requiring prolonged mechanical ventilation. It is now available in generic form.

Propofol (Diprivan) is an anesthetic agent with very rapid onset (minutes) and short duration of action (minutes) which is given as a continuous infusion (0.3-0.8 mg/kg/hr). The delivery vehicle is a fat emulsion. At commonly used infusion rates, patients can receive the equivalent of around 500 ml of Intralipid per day (550 kcal). The fat emulsion is a good microbial growth media and strict aseptic technique and changing of i.v. tubing, etc every 12 hours is required. Diprivan has been reformulated (to extend its patent) by including EDTA as a preservative. An alternative formulation of propofol is now available from Baxter, but differs in that it contains bisulfite as preservative (88). Despite the potential for commercial competition, propofol remains the most expensive sedation agent (see below). Pain at the injection site is common but is usually avoided by infusing through a central line.

Apnea occurs frequently, but may help facilitate mechanical ventilation. Hypotension and bradycardia are also common, but primarily when the drug is given as a rapid bolus. As with the benzodiazepines, propofol has no analgesic effect; amnesia is less reliable, except at high doses. Hypertriglyceridemia occurs, as does pancreatitis (see below). The drug has both anti- and pro-convulsant properties, depending upon the dose, in patients with seizure disorders (see below). Propofol is no longer used in pediatrics as a fatal syndrome (the "propofol syndrome") of progressive metabolic acidosis, myocardial failure (hypotension, bradycardia, heart block, asystole), lipemic serum, and fatty infiltration of the liver has been described in children under the

age of 12 years (89,90). Propofol is generally used for short-term use, especially post-operatively for CABG. It may be advantageous for use during procedures, to allow for frequent neurologic assessment, or to tide a patient over for a brief interval after other agents such as midazolam have been stopped in anticipation of extubation.

Opiate analgesics are frequently used in combination with a sedative agent for control of pain. Morphine is usually given either as intermittent bolus (1-2 mg) or by continuous infusion (1-4 mg/hr). Its onset is rapid (2-3 min) and it has a duration of action of 4-5 hours. Morphine metabolites have active sedative and analgesic properties. It may stimulate histamine release and may cause hypotension. Fentanyl is a short-acting opiate that is far more potent than morphine. It is usually given as an infusion (50-100 μg/hr). It has limited cardiovascular effects and no active metabolites. Both can impair GI motility and limit enteral alimentation (91,92).

Haldoperidol is a butyrophenone neuroleptic. Agitation often is caused by delirium rather than being a manifestation of anxiety or lack of sedation; ICU conditions are particularly conducive to confusional states and delirium (93-95). Haldoperidol can be very effective in controlling agitation. It can be used alone or in combination with other agents. The usual dose is commonly cited as being 1-4 mg/hr (either intermittent bolus or continuous infusion). However, when used in this context, significantly higher doses may be needed and are appropriate. Doses of up to 25-40 mg/hr have been reported (96,97). Haldoperidol potentiates the analgesic effects of opiates. Tardive dyskinesia and neuroleptic malignant syndrome can occur.

The use of multiple agents in varying combination is often advocated. Sedation, pain, and agitation can be managed independently. As these agents have different mechanisms of action and target receptors, synergism is often noted with combined therapy (34,78). This usually allows substantial reduction in the doses of individual agents (and thus potential cost sparing as well).

A comparison of the daily direct cost for these drugs is shown below. This is based upon data at the Dallas VA Medical Center as of March, 2001. The infusion rates used for the calculations come from average doses in published clinical studies involving primarily medical ICU patients requiring mechanical ventilation (20,21,31,74,79,96).

Average Daily Cost for Continuous Infusions:
Dallas VA Medical Center
March, 2001

Drug	Infusion rate (mg/kg/hr)	Infusion rate (mg/hr)	Drug Cost ($/ day)
propofol (Diprivan)	2.5	175	218
propofol (Baxter)	2.5	175	151
midazolam	.15	10	68
lorazepam	.06	4	33
haldoperidol	.06	4	93
morphine	.03	2	17
fentanyl	.001	.075	2

The majority of published information relating to the safety, efficacy, kinetic and pharmacodynamic properities of these drugs comes from the anesthesia literature and the data is largely based upon the use of these drugs in otherwise healthy individuals undergoing elective surgery. In most cases, the drugs are used either for induction alone or for short-term (minutes to hours) continuous infusion. Many of the published review articles, even in critical care literature, base recommendations for choice of drug and dosing upon such data. This often results in significant misunderstandings about the behavior and use of these same agents in critically-ill patients. Those caring for such patients recognize that, in general, medical ICU patients: (1) require significantly higher doses, (2) exhibit greater inter-patient variability with respect to dosing requirements, and (3) remain sedated for significantly longer periods after cessation of drug administration.

Mean dosing requirements from studies of healthy subjects and patients undergoing elective surgery (usually CABG) are fairly modest, e.g. propofol 0.7-1.6 mg/kg/hr (76-78,80,81); midazolam 0.02-0.08 mg/kg/hr (76,78,80). In contrast, mean doses reported in studies of ICU populations (MICU, trauma) are considerably higher: propofol 2.0-2.8 mg/kg/hr (73,75,79); midazolam 0.22-0.24 mg/kg/hr (20,74).

Mean Dosing Requirements for Continuous Sedation in Different Patient Populations

	Propofol (mg/kg/hr)	Midazolam (mg/kg/hr)
Elective Surgery	0.7-1.6	.02-.08
MICU / Trauma	2.0-2.8	.22-.24
MICU + Morphine	1.5-2.0	.03-.17

In part, this explained by the fact that post-operative patients are recovering from deep anesthesia and continue to receive fairly high doses of concomitant opiate

analgesics. Concurrent infusions of opiates have synergistic effects as noted earlier and result in lower mean dosing requirements in MICU patients as well: propofol 1.5-2.0 mg/kg/hr (84); midazolam 0.03-0.17 mg/kg/hr (79,84). Also, the higher dosing requirements in MICU patients are in part explained by the use of more complex modes of ventilation in patients with severely altered lung mechanics, especially those with obstructive lung disease or ARDS (98-101). Tolerance during prolonged infusions has been seen with both benzodiazepines and propofol (75).

In addition to having generally higher drug requirements, MICU patients typically also show greater inter-patient variability with respect to drug efficacy and dose (44). Indeed, serum drug levels correlate very poorly with level of sedation in this population in particular, especially with benzodiazepines (44,47,102,103). Reasons for this extreme variability include patient characteristics such as age, obesity, and prior drug/alcohol use. The effects of critical illness undoubtedly also play a role. Drug receptor affinity, local compartmental alterations in pH or membrane states, co-existing CNS dysfunction, and drug interactions may all play a role.

Critically-ill patients also demonstrate significantly longer duration of sedation when compared to anesthesia applications. While this can be observed with virtually all sedation/analgesia agents, it is particularly true for the benzodiazepines and opiates (including fentanyl). Patients may remain completely sedated for many days after stopping all agents, significantly prolonging the duration of mechanical ventilation and ICU length-of-stay. With this comes the potential for higher complications, use of diagnostic studies, and cost (see above).

There are numerous potential causes for prolonged sedation in these patients, independent of the "baseline" clinical half-life of each drug (lorazepam > midazolam > propofol). Failure to recognize and treat correctable causes of agitation may lead to over-sedation. Drug tolerance has been observed with each. Patients may remain comatose even after all drug has been eliminated owing to co-existing intra-cerebral conditions, metabolic disorders, or hepatic/uremic encephalopathy which have developed, unrecognized, during active sedation.

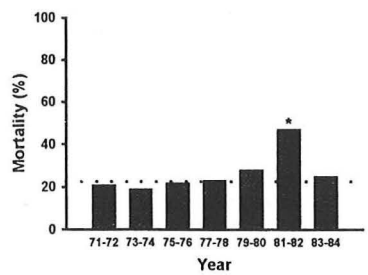
Drug accumulation during prolonged infusion is common (48,49) in part due to the extremely large apparent volume of distribution observed in critically-ill patients (40,43), especially those with cirrhosis or sepsis. Most of these agents are extremely lipophilic and obesity contributes to drug accumulation (53,54). Most also exhibit significant protein binding (52,53,65) and thus changes in serum proteins during severe illness may also contribute. Some of these agents also have active metabolites, especially midazolam, which can also accumulate during prolonged infusion (49-51). Drug clearance may be impaired in the presence of liver (46,48,50) or renal dysfunction, especially with midazolam and

opiates. Drug interactions and CNS depressant effects of other medications, alterations in cytochrome P450 iso-enzyme function, and patient age (54) may also play a role.

To some extent, many of these problems are inherent to the underlying disease process and therefore unavoidable. In general, problems with prolonged sedation have been more commonly reported with lorazepam and midazolam as compared to propofol. However, there are data that careful attention to dose titration may minimize or even eliminate these problems such that each of the commonly used agents may be comparable with respect to clinical and cost effectiveness (see below).

In addition to the kinetic and pharmacodynamic variations noted above, these agents may also exhibit some unusual and unexpected effects. One of these is illustrated by the early experience with etomidate, an anesthetic agent which is still used for anesthesia induction and airway intubation because of its very rapid onset, short duration of action, and minimal effects on hemodynamics. When it was first introduced, it was hoped that it would be useful for long-term ICU sedation when given as a continuous infusion. The drug began to be used in many patients requiring mechanical ventilation in a trauma ICU in Glasgow in 1981 (104). In prior years the overall mortality was consistent and between 19-29%; however in 1981 it was 47% ($p<.05$). It was observed that all of the excess mortality occurred in patients who had been sedated with etomidate. Mortality was 77% in 27 patients receiving etomidate and 28% in 50 sedated with benzodiazepines ($p<.0005$). The increase was not explained by differences in patient demographics or severity of illness at the time of admission.

Excess Mortality in Trauma Patients Treated with Continuous Infusion Etomidate
Watt and Ledingham, Anaesthesia 39: 973 (1984)

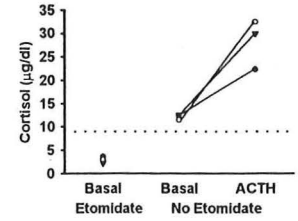


Most of these patients appeared to have died from multiple organ failure, with a high incidence of sepsis. One explanation for the observed excess mortality was the possibility of adrenal suppression. The study was retrospective and non-randomized; no data were available with respect to adrenal function in the benzodiazepine group. Cortisol determinations were made in 17 of the 27 etomidate patients; all 17 had levels below the "normal" basal level of 9 μg/dl and

10 had severely depressed cortisol levels (< 4 μg/dl), especially for "stressed" ICU patients. The use of etomidate was eliminated. Overall mortality returned to expected levels in the subsequent 2-year period; cortisol levels measured thereafter were normal (of those measured, all > 9 μg/dl and 78% > 20 μg/dl).

Several other reports had shown that the normal adrenocortical response to surgery was suppressed by the use of etomidate infusion (105-107). Fellows, et al had found low levels of plasma cortisol in 6 surgical patients who exhibited clinical features of adrenal insufficiency (106). This was not due to primary adrenal dysfunction as basal and ACTH-stimulated cortisol levels returned to normal within 3 days of discontinuing etomidate.

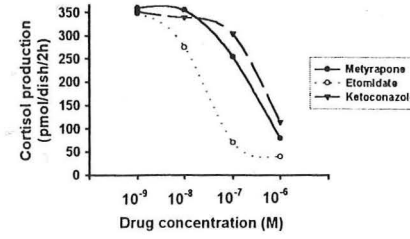
Adrenocortical Function in Trauma Patients During and After Discontinuation of Etomidate Infusion
Fellows, et al, Br Med J 287: 1835 (1983)



Plasma ACTH levels were appropriately elevated during etomidate infusion when cortisol was low (106). Others had shown that norepinephrine levels were not affected (107). These observations suggested that etomidate suppresses adrenal gland synthesis and/or secretion of corticosteroids.

At about the same time, adrenal suppression was being recognized in patients treated with the anti-fungal agent, ketoconazole (108,109), though the effects were greatest with respect to testicular function. The two drugs are related, both being imidazole derivatives (110). Both suppress the *in vitro* synthesis of cortisol by hyperplastic adrenal cells from patients with Cushing's syndrome; in fact, etomidate is more suppressive than either ketoconazole or metyrapone (111).

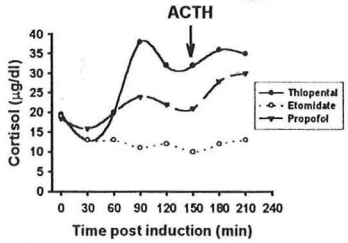
Suppression of Cortisol Synthesis by Hyperperplastic Adrenal Cells in the Presence of ACTH
Lamberts, et al, J Pharm Exp Ther 240: 259 (1987)



Subsequent studies have shown that etomidate acts primarily through inhibition of 11-β-hydroxylase, the terminal step in the production of cortisol. Ketoconazole acts at a more proximal level, primarily inhibiting C17,20-desmolase (although it also suppresses 11-β-hydroxylase to some extent), thus explaining its greater effect on testicular function (110).

Although these observations relative to etomidate's suppressive effect on adrenal function led to the discontinuation of its use for continuous infusion as an ICU sedation agent, it is still used as a single injection for anesthetic induction and airway intubation. Even a single a dose of etomidate will produce measurable effects on adrenocortical function (107,112). The effect appears to be a blunting of the response to ACTH. The effect lasts at least 4 hours (112). There are no reports of significant clinical consequences to a single dose of etomidate.

Adrenocoritical Function After Single, Induction Dose of Thiopental, Etomidate, or Propofol
Fragen, et al, Anesthesiology 66: 839 (1987)

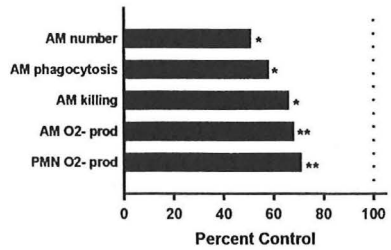


Some observers have reported a measurable effect of propofol on ACTH-stimulated cortisol production (112-114). However, others have found no significant effect of propofol on adrenal function (58,80,81,115) and there are no published reports of clinically significant adrenal suppression. Midazolam does not effect adrenal function (81).

Another potential explanation for the excess mortality observed with continuous etomidate infusion is that the increased incidence of sepsis was the result of more specific drug effects upon immune function. Indeed, there is considerable evidence that many of the agents used for sedation/analgesia have immune modulatory effects (116-121).

Tubaro, et al found that morphine given for 3-6 days to rabbits resulted in a significant reduction in alveolar macrophage (AM) number; suppression of AM phagocytosis and killing of *C. albicans*; and diminished AM and PMN superoxide generation (122). This was associated with decreased lymphoid organ mass and susceptibility to *Klebsiella pneumoniae* and *Candida albicans* infection. Although the doses of morphine appear to be quite high in this study, they are cominsurate with the doses required in small animals to mimic the other pharmacologic effects of opiates effects in primates and humans.

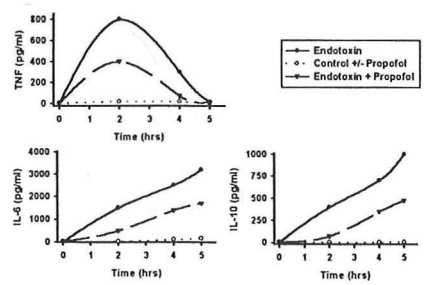
Suppression of Alveolar Phagocyte Number and Function by Morphine in Rabbits
Tubaro, et al, J Infect Diseases 148: 656 (1983)



*Morphine 50 mg/kg sc bid X 3d; p<.001
**Morphine 85 mg/d X 6 days; p<.01

Taniguchi, et al studied the effects of propofol on the inflammatory response to endotoxemia in rats (123). They found that treatment with propofol at doses similar
to that expected in humans during sedation significantly depressed circulating cytokine production (tumor necrosis factor, interleukin-6, and interleukin-10). Propofol also had a modest effect upon endotoxin-induced PMN infiltration of lung as assessed histologically.

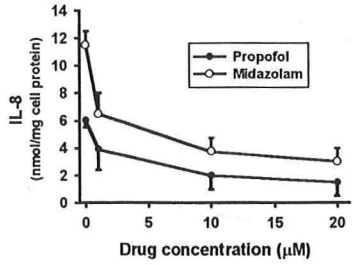
Propofol Suppression of Inflammatory Responses to Endotoxin in Rats
Taniguchi, et al, Crit Care Med 28: 1101 (2000)



Galley, et al demonstrated that both propofol and midazolam suppress LPS-stimulated production of interleukin-8 from human PMNs (124). Extra-cellular IL-8 accumulation was reduced, but intra-cellular IL-8 and IL-8 mRNA were high, suggesting that these agents prevent IL-8 secretion. It is not clear that propofol's pharmacologic effects are entirely due the drug itself as it is delivered in an intravenous fat emulsion, which is essentially the same as the fat emulsions used for TPN (e.g. Intralipid).

The independent effects of the fat emulsion must be included in any discussion of propofol. Intravenous fat emulsions (IVFE) increase oxygen consumption, carbon dioxide production and thus minute volume requirements. IVFE can cause alterations in gas exchange (125,126), including V/Q mismatching, diffusion impairment, and overt intra-pulmonary shunt (especially in ARDS). Prostaglandin synthesis and surfactant production are both affected by IVFE

Suppression of LPS-Stimulated IL-8 Production from Human PMNs *in vitro*
Galley, et al, Anesth Analg 86: 1289 (1998)



(126). Recent studies have shown that propofol has *in vitro* anti-oxidant properties (127); this effect may well be a property of the IVFE rather than the drug itself.

IVFE are also associated with increased susceptibility to infection and immune modulation (128-130). The emulsion is very supportive of microbial growth, requiring frequent changes of tubing and delivery containers. The currently available formulations of propofol include either EDTA or bisulfite as preservatives, but these are not bacteriostatic or bacteriocidal.

Battistella, et al conducted a randomized trial in trauma patients comparing total parenteral nutrition (TPN) alone or with IVFE (128). They found that patients who received TPN + IVFE experienced 2.4 infections per patient as compared to 1.4 infections per patient in the TPN alone group. There were approximately twice as many cases of pneumonia and line sepsis in the group receiving IVFE. The patients were similar with respect to demographics and severity of illness; there was no difference in mortality. T-cell function in these patients was assessed by lymphokine-activated killer cell activity (LAK) and natural killer activity (NK). They found no significant effect in the TPN alone group, but there was significant depression of both LAK and NK activity on day 5 as compared to the day of randomization in the TPN + IVFE group.

Infectious Complications with Intravenous Fat Emulsion (Intralipid) in Trauma Patients
Battistella, et al, J Trauma 43: 52 (1997)

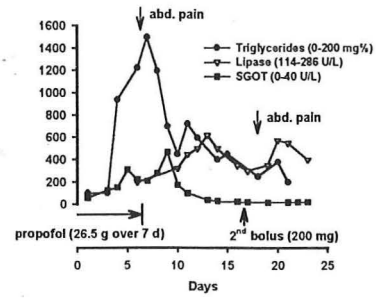
	TPN Alone (n=27)	TPN + Lipid (n=30)	
Infections (per pt)	1.4	2.4	
LAK activity (day_5/day_0)	1.20	.65	p=.05
NK activity (day_5/day_0)	1.40	.45	p=.04
CD_4 / CD_8 (ratio)	2.1	2.0	n/s

IVFE has also been associated with hypertriglyceridemia and pancreatitis (131,132). Propofol infusions also produce hyperlipidemia, especially with long-term administration, in patients with coexisting lipid disorders, and/or when IVFE is given concomitantly as part of TPN (60,75,133). Generally, serum triglycerides are only modestly elevated, at about 200 mg/dl (75), but severe elevations and lipemia can occur. In one study propofol was discontinued in 20% of patients because of severe hypertriglyceridemia (>500 mg/dl); women were affected more commonly than men (85).

Propofol has been associated with pancreatitis as well (134-136). Between its indroduction in 1989 and 1999, 25 cases of pancreatitis associated with propofol have been reported through the FDA's self-reporting system (136). Although severe hypertriglyceridemia is generally accepted as causing pancreatitis (131,137), the role of hypertriglyceridemia is less certain in the case of propofol. In some cases serum triglycerides were less than 500 mg/dl (134) and in others were not reported (135).

One case is particularly interesting. Kumar, et al reported a patient who developed abdominal pain and tenderness after receiving 26.5 g of propofol over

Propofol, Hypertriglyceridemia, and Pancreatitis
Kumar, et al, Chest 115: 1198 (1999)



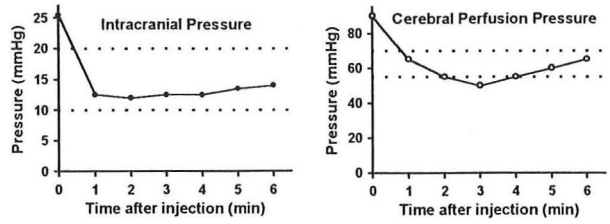
7 days (approximately 2.25 mg/kg/hr) during mechanical ventilation for pneumonia. She had no history of prior pancreatititis, alcolhol use, or cholecystitis; she had received no other drugs associated with pancreatitis. Serum lipase peaked at 622 U/L (normal 114-286 U/L). Serum triglycerides were normal at admission, but were 1498 mg/dl (normal <200 mg/dl) at the time of abdominal pain. An abdominal sonogram showed evidence of pancreatic inflammation, but normal liver and bile ducts. However, there were small stones in the gallbladder and both serum SGOT (peak 475, normal <40 U/L) and alkaline phosphatase (peak 305, normal <136 IU/L) were elevated during the acute episode. Abdominal pain resolved, liver function tests normalized, and serum triglycerides fell after discontinuing the propofol. Interestingly, the patient inadvertently received a single 200 mg bolus of propofol on day 17 as part of anesthesia for tracheostomy revision. This was associated with recurrence of abdominal pain and re-elevation of serum lipase (peak 564 U/L). At this time, liver function tests remained normal and serum triglycerides were only 380 mg/dl. While the first episode may have been due to choledocholithiasis, the second episode is more convincing and also suggests that the cause may be propofol itself rather than hypertriglyceridemia.

Propofol has several potential advantages for use in patients with neurologic dysfunction. Its short duration of action allows for more frequent assessment of neurologic function during intermittent periods of drug cessation. It decreases cerebral metabolism and oxygen utilization. When given before or during (but not after) ischemic or mechanical brain injury, propofol may have neuroprotective effects, at least in animal models (138,139). Its role in patients with increased intracranial pressure (ICP) or seizure disorders has been the subject of some controversy, however.

Animal studies have shown that propofol may reduce ICP in models of space-occupying lesions, though not in the case of whole-brain edema (140). The presumed mechanism is that propofol reduces cerebral metabolism, which in turn leads to decreased cerebral blood flow (if autoregulation remains intact); this would decrease intracranial blood volume and thus ICP (140). Based upon clinical comparisons between propofol and morphine for sedation of patients with severe head injury, some have suggested that propofol may be desirable because of its better effect on ICP (141).

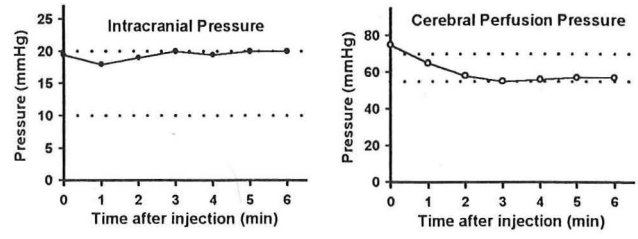
Others have consistently reproduced the observation that bolus injection of propofol will reduce ICP when it is significantly elevated (142,143). However, in these patients propofol also causes depression of mean arterial blood pressure (MAP). Since cerebral perfusion pressure (CPP) is determined by both MAP and ICP (CPP = MAP – ICP), the improved ICP is offset by reduction in MAP. Indeed, in most reports, the effect on MAP exceeds the beneficial effect on ICP such that CPP is significantly reduced, often below recommended levels (142,143). Thus, bolus injection of propofol should be used with caution in this situation.

Propofol and Intracranial Hypertension
2 mg/kg i.v. over 90 sec
Herregods, et al, Anesthesia 43 (sup): 107 (1988)



Similar studies with midazolam have shown that it does not lower ICP, but does reduce MAP and thus CPP. Bolus injection of midazolam should also be avoided in patients with increased ICP.

Midazolam and Intracranial Hypertension
0.15 mg/kg i.v. over 60 sec
Papazian, et al, Br J Anaesth 71: 267 (1993)



Propofol has also been associated with seizures in some clinical case reports (144-147), though this has not been reported in larger series. Seizures have generally been reported during propofol sedation, though in one case status epilepticus developed 6 days after discontinuing propofol (71). Most patients have had underlying seizure disorders; seizure activity is generally described as classic tonic-clonic movements, and some have had concurrent EEG documentation of epileptiform activity. However, not all cases have EEG evidence of seizures and some reports describe myoclonic activity, opisthotonos, or other "abnormal involuntary movements" which may not be true seizures. Seizures have been described after both prolonged infusions as well as brief anesthetic doses (144).

Although these reports provoked concern about the potential pro-convulsant effect of propofol, it is actually recommended for treatment of severe, refractory status epilepticus (148). In animal models, propofol inhibits seizures evoked by both electroshock (149) and lidocaine (150). Furthermore, propofol shortens the duration of both physical and electrical seizure activity in patients undergoing electroconvulsive shock therapy when compared to other short-acting anesthetic agents (151,152).

Careful studies have been done in neurosurgical patients at this instituition (153), as well as in patients undergoing surgery for intractable epilepsy (154,155). Incremental doses of propofol were given during continuous EEG monitoring. At low doses (0.6-1 mg/kg) there is evidence of EEG activation. However, at higher doses (>1.5 mg/kg) EEG activity, including epileptiform activity, is suppressed. Thus, propofol likely is safe at doses generally used for ICU sedation, even in patients with seizure disorders, though it would seem prudent to discontinue the drug should seizures develop during therapy.

A conspicuous problem with sedation in the ICU is the difficulty in defining and achieving an optimum level of sedation/analgesia. Fixed dosing is inappropriate given the wide inter-patient variability described above. Some providers strive for achieving a quiet, relaxed patient, while others are more interested in producing sleep or even "chemical restraint" (23).

Newer modes of ventilation which emphasize the lung protective strategy, which have afforded improved survival in ARDS (100,156), also often necessitate deeper degrees of sedation in order to minimize respiratory system compliance (especially chest wall), facilitate patient-ventilator co-ordination, and combat the enhanced respiratory drive inherent in permissive hypercapnia (98-101). These modes may also necessitate the use of neuromuscular blockade, with its inherent complications, including the potential for "awake paralysis" (1,3,157).

Inconsistency in dosing and assessment is common due to wide variations in both intra- and inter-observer variability, skill, and training. Deeper levels of sedation are often observed in units subjected to understaffing (23). Over-sedation can occur as well in the absence of defined protocols or when assessment of sedation level is performed infrequently. As noted earlier, failure to seek correctable causes of agitation or to discriminate between sedation, agitation, and pain also contribute to the problem.

The use of standardized protocols for administration of ICU sedation/analgesia should, by definition, provide greater consistency. Studies have demonstrated that the implementation of such protocols consistently reduce total drug use and pharmacy costs (158). More importantly, adherence to careful assessment of level of sedation with defined goals has to produced shorter awakening times and reduced duration of mechanical ventilation and ICU stay (84,159).

There are a variety of methods for assessing the need for sedation in ICU patients including simple clinical observation and routine physiologic variables. Tachycardia and hypertension, though certainly not specific, are markers of anxiety, pain, and agitation. The commonest method for attempting to provide a more uniform and at least semi-quantitative method for assessment has been to use one or more of the numerous clinical sedation scales which have been described (160-164). Perhaps the most utilized was the first to be described, the Ramsay Sedation Scale (160). This was adopted for anesthesia research purposes and has been widely used in ICU settings as well.

Ramsay Sedation Scale
Ramsay, et al, Br Med J 2: 656 (1974)

1	**Anxious, agitated, or restless**
2	**Cooperative, oriented, tranquil**
3	**Responds to command only**
4	**Brisk response to light glabellar tap**
5	**Sluggish response to glabellar tap**
6	**Unresponsive**

Riker, et al introduced and later modified the Sedation-Agitation Scale, which is intended to more appropriately describe ICU patients, in particular by providing greater discriminate power for various degrees of agitation (161). Their scale has been validated in ICU patients and is now widely used; we have adopted this scale in our MICU at the Dallas VA Medical Center.

Modified Sedation-Agitation Scale (S.A.S.)
Riker, et al Crit Care Med 27:1325 (1999)

7	Dangerous agitation	Pulling ETT/ lines, climbing out of bed, thrashing, hitting staff
6	Very agitated	Will not calm, requires restraints, biting ETT
5	Agitated	Anxious, agitated, but calms with verbal instruction
4	Calm, cooperative	Calm, awakens easily, follows commands
3	Sedated	Responds slowly to verbal or gentle stimulation, follows commands
2	Very sedated	Responds to physical stimulation but does not follow commands
1	Unarousable	Minimal or no response to noxious stimuli

Observers have found that when questioned after their stay in the ICU, many patients complain in particular about the level of pain and discomfort they experienced (4,8). The use of concomitant analgesia has thus become commonplace and has had synergistic effects with other agents. Separate assessment of pain, e.g. using an analog visual scale from 1-10 for patients to rate their current level of pain have been advocated and may prove valuable.

While relatively simple and inexpensive, these assessment tools are inherently only semi-quantitative and highly observer-dependent (165,166). Furthermore, they cannot be used to assess sedation or analgesia in the paralyzed patient. For these reasons, there have been attempts along several lines to used quantifiable physiologic variables to assess sedation.

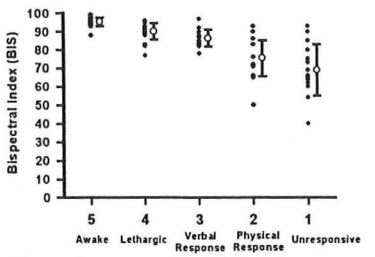
For example, R-R variability of heart rate (slowing, regularization with increasing sedation) has been shown to correlate with the Ramsay Sedation Scale (167). While this technique may be superficially attractive and the software tools for this are part of many of the newer ICU cardiac monitoring systems, it has limited practical value. It is highly non-specific as many other factors will affect R-R variation, including pain, sepsis, fever, hypoxia, drugs (e.g. β-blockers, calcium channel blockers, digoxin), technical artifact, and of course the presence of dysrhythmias. Auditory evoked potential monitoring has been used in research settings, but has no practical value in ICU patients (164,168).

Neurophysiologic monitoring systems which rely upon EEG have been described (169). Although continuous, standard EEG has been used for research applications (102,170,171), it is of no practical use for clinical application in the ICU setting as it is inherently unstable technically and would require the full-time attention of a trained neurologist. EEG is a highly complex signal whose proper interpretation is highly qualitative and it is affected by technical problems such as stability of leads, EMG, and the electrical "noise" which abounds in the ICU environment. Efforts to simplify the EEG output by various filtering techniques coupled with high-order mathematical computer-processing led to early modifications of EEG which have been used fairly extensively in anesthesia research, as well as in the ICU (172,173). These used time-domain analysis of the EEG signal or frequency spectral analysis. There were difficulties in defining the appropriate index to be used in such analysis (e.g. peak or median frequency intensity, "leading edge" frequency, etc). Unfortunately, some of these techniques were still fairly qualitative and it was observed that univariant descriptors such as median or "leading edge" frequency demonstrated significant phase-dependency, limiting their interpretation and use in general clinical settings. Furthermore, these techniques are expensive and technically challenging (169,174).

- A fairly recent innovation is the development of an EEG-based multivariant index, the bispectral index, or BIS (175). BIS is commercially available and analyzes continuous EEG signal from a simplified frontal montage of electrodes placed over the patient's forehead. Computerized 3rd order spectral analysis yields a single value, the BIS, which ranges from 100 (fully awake) to 0 (total EEG suppression). Generally, the vendor suggests that levels from 100 to 70 represent wakefulness, 70-60 light hypnotic effect (low probability of recall, "conscious" sedation), 60-40 moderate hypnotic effect (unconsciousness), and below 40 deep hypnotic effect (anesthesia). These recommendations derive primarily from correlations between BIS and clinical sedation scales, especially in

healthy volunteers and patients undergoing anesthesia (103,176). The BIS has also demonstrated at least statistical correlation with clinical sedation scales in ICU patients on mechanical ventilation (98,177).

Bispectral Index (BIS) EEG Monitoring During Sedation with Midazolam
Liu, et al, Anesthesiology 84: 64 (1996)



Unfortunately, it is difficult to know if the added expense and technical complexity will prove to be of benefit in the general ICU population. It has only been "validated" against clinical sedation scales (which are obviously already available with virtually no additional cost) and there are as yet no outcome-based studies to suggest superiority over clinical assessment. Furthermore, as one writer has admitted, "...no one truly understands what physiologic phenomena the BIS measures..." (178).

BIS might prove to be an attractive mode for assessing an important sub-group of ventilated patients, namely those receiving neuromuscular blockade, since clinical assessment is not possible unless paralytics are stopped (which may not be possible or desirable). It has been observed that the level of sedation achieved in paralyzed patients as assessed by BIS is significantly deeper (i.e. lower BIS) as compared to non-paralyzed patients. While this in part reflects the clinician's need to achieve deeper sedation in sicker patients with more complex modes of ventilation (e.g. to minimize the degree of neuromuscular blockade), it has also been suggested that these patients are being "over-sedated". If true, one would target higher BIS levels in paralyzed patients, in the hopes of preventing prolonged sedation effects once weaning is feasible.

Unfortunately, recent observations in paralyzed patients suggest that this might be a scary tactic. Cheng, et al reported that the mean BIS of a small number of patients who were paralyzed was 57% that of another group of non-paralyzed patients (179). Importantly, it was also shown that this reduction in BIS was associated with a similar reduction in EMG activity, suggesting that the BIS is reduced principally through neuromuscular block's ablation of EMG signal which is detected in the BIS. Thus, if patients were titrated to recommended BIS levels, they might well be awake, though paralyzed. Until further work is done

specifically in paralyzed patients determining appropriate levels of BIS-measured sedation, one cannot recommend it for this purpose.

Bispectral Index (BIS) Monitoring of Ventilated Patients With and Without Neuromuscular Blockade
Cheng, et al, Anesthesiology 91 (sup): B13 (1999)

	Sedated (n=4)	Paralyzed (n=3)
BIS	70	40
EMG	12.8	5.4
SQI	84	84

In the early 1980's it was commonplace for patients on mechanical ventilation to be maintained in a state of deep sedation, unarousable, and unaware of their surroundings (23). As noted above, more recent trends have emphasized the problems associated with over-sedation and have recommended lighter target levels for maintaining sedation (23,180,181). One recent study emphasizes the potential importance of the "less is more" approach and represents one of the more carefully performed studies of the use of ICU sedation agents.

Kress, et al from the University of Chicago sought to test the hypothesis that daily interruption of sedation infusions might improve clinical outcome in mechanically ventilated patients (84). MICU patients who were receiving mechanical ventilation and who were deemed to require continuous sedation by their primary physicians were randomly assigned to either the intervention (daily awakening) or control group. Each group was also randomly divided into a standardized treatment protocol with either propofol or midazolam.

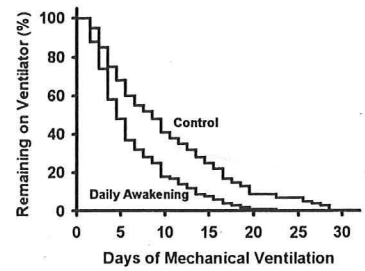
In the intervention group, members of the study team performed a daily interruption of sedation (daily awakening) beginning 48 hours after intubation. Sedation was held (stopped completely) until the patient became awake or showed signs of agitation. At that time an assessment of patients' mental status was performed. Then sedation was restarted, but at one half the prior infusion rate. If the patient had been receiving paralytic agents (11% of patients enrolled), these were stopped and restoration of neuromuscular transmission (4/4 "train-of-four") was demonstrated before interrupting sedation. The control group was managed similarly with the exception that there was no daily awakening.

In all patient groups, medical management was performed by the primary ICU team. All patients received concomitant morphine for analgesia according to protocol. Sedation agents (propofol or midazolam) were delivered and adjusted by the nursing staff (not the investigators) according to protocol with a target level

of sedation corresponding to a Ramsay Sedation Scale score of 3-4 (sedated but responsive).

The most important result of the trial was that patients in the daily awakening group had significantly shorter duration of mechanical ventilation and ICU length of stay; on average the control group spent 2.5 days longer on the ventilator. No significant effect was seen with respect to mortality, but the study was not designed to have sufficient statistical power for this purpose.

Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation
Kress, et al, N Eng J Med 342: 1471 (2000)



Importantly, the shortened duration of mechanical ventilation was achieved without accompanying increase in complications such as self-extubation or loss of i.v. lines. One other important benefit of the daily awakening approach was that only 38% as many studies were performed to assess altered mental status (head CT, MRI, lumbar puncture).

Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation
Kress, et al, N Eng J Med 342: 1471 (2000)

	Daily Awakening (n=68)	Control (n=60)	p
Time on vent (d)	4.9	7.3	.004
ICU LOS (d)	6.4	9.9	.02
Mortality (%)	36	47	.25
Lost ETT, line (n)	3	4	n/s
Head CT,MRI,LP (n)	6	16	.02

That the avoidance of over-sedation was responsible for the improved outcome was demonstrated by the fact that the daily awakening group received significantly less total sedation and analgesia. Importantly, this reduction in total drug administration occurred in the midazolam, but not the propofol, subgroup.

When the various outcome measures were assessed by comparing all patients who received propofol to those receiving mizaolam, there were no significant differences.

Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation
Kress, et al, N Eng J Med 342: 1471 (2000)

	Daily Awakening (n=68)	Control (n=60)	p
Midazolam (n)	37	29	
Total midazolam (mg)	230	426	.05
Total morphine (mg)	205	481	.06
Propofol (n)	31	31	
Total propofol (g)	15.1	17.6	.54
Total morphine (mg)	352	382	.33

Midazolam vs Propofol: no difference for major endpoints.

This study allows several important conclusions to be drawn. Avoidance of over-sedation is: (1) achievable, (2) safe, (3) improves outcome, and (4) reduces resource utilization, including diagnostic studies. Furthermore, this study clearly demonstrates that for purposes of avoiding over-sedation and limiting duration of mechanical ventilation, the specific choice of sedation agent is of secondary importance as long as the primary goal is to achieve minimum required sedation.

While this study did not show any adverse effect of limiting sedation, some have expressed concern that limiting sedation (especially daily awakening) might have unintended adverse effects, e.g. on psychological well-being or cardiovascular function (22,181,182). Although this study achieved improved outcome using once-daily awakenings, others (including the authors themselves) have suggested that the specific method used may not be as important as focusing upon the primary goal of avoidance of over-sedation (181). For example, it might be possible to achieve similar results with continuous infusion and careful attention to limiting sedation to minimum required dose. This might be accomplished by periodically cutting the infusion rate in half or even intentionally cutting to the minimum tolerated dose, mitigating the potential adverse effects of full awakenings.

Providing sedation can be beneficial, but is not without clinical cost. In providing sedation, we should keep in mind the varied actions of these agents and recognize that ICU patients have very different pharmacokinetics compared to anesthesia applications. Dosing must be individualized and titrated to clinical effect, guided by protocol, and using a clinical sedation scale. The specific choice of agents should be influenced by the desired clinical effect (sedation, analgesia, vs control of agitation) as well as clinical context and co-existing conditions. Although no uniform "ideal" level of sedation exists, it is clear that we should be making a conscientious effort to limit sedation to the minimum necessary level.

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