Review

Life-threatening brain failure and agitation in the intensive care unit

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Abstract

The modern intensive care unit (ICU) has evolved into an area where mortality and morbidity can be reduced by identification of unexpected hemodynamic and ventilatory decompensations before long-term problems result. Because intensive care physicians are caring for an increasingly heterogeneous population of patients, the indications for aggressive monitoring and close titration of care have expanded. Agitated patients are proving difficult to deal with in nonmonitored environments because of the unpredictable consequences of the agitated state on organ systems. The severe agitation state that is associated with ethanol withdrawal and delirium tremens (DT) is examined as a model for evaluating the efficacy of the ICU environment to ensure consistent stabilization of potentially life-threatening agitation and delirium.

Keywords: alcohol, central nervous system, delerium tremens, detoxification, ethanol withdrawal

Introduction

The major etiology of integrative brain failure is a hemodynamic or metabolic decompensation elsewhere in the body [1•]. The ICU environment provides a repository of typical predisposing factors of a hemodynamic or metabolic nature, including acute or chronic organic brain vascular insufficiency, endocrine insufficiency, acute or chronic cardiopulmonary decompensations, multiorgan system insufficiency, relative hypoxia, poor tissue perfusion, multimedications, and, finally, sleep–wake cycle disruption caused by immobilization, anxiety and pain [2]. Clinical signs of agitation are likely to be produced when there is integrative brain failure plus an intense source of sensory stimuli [3]. Environmental stress, although likely to exacerbate integrative brain failure, is rarely a precipitating cause by itself [4]. When agitation accompanies brain failure in a critical care setting, a failure to integrate cerebral functioning exists, and this constitutes a true emergency.

Agitation is a visual clue that disintegration of normal motor axis integration is occurring, with mischanneling of incoming sensory stimuli [5•]. There is growing consensus that delirium is a manifestation of cerebral insufficiency, both generalized and focal, that is accompanied by dysregulation of neurotransmitter systems. Short circuits into phylogenetically old brain areas such as basal ganglia, reticular formation, vestibular nuclei, and often the red nucleus (extrapyramidal system) produce the clinical picture of uncoordinated and nonpurposeful movements [6•]. Delirium is characterized by global disorders of cognition and wakefulness, and by impairment of psychomotor behavior. Major cognitive functions such as perception, deductive reasoning, memory, attention and orientation are all globally disordered. Excessive motor activity frequently accompanies severe cases of delirium and, when this occurs, the resulting constellation of symptoms is called ‘agitated delirium’.

CNS = central nervous system; DT = delirium tremens; GABA = γ-aminobutyric acid; ICU = intensive care unit; NMDA = *N*-methyl-D-aspartate.

Generally, such episodes are indicated by escalating agitation in the face of increasing sedative administration and the addition of multiple drugs. Eventually, a point is reached at which the underlying causes of agitation, combined with side effects of pharmacologic agents, threaten respiratory and hemodynamic stability. The mortality of severe delirium has been exacerbated in the past by respiratory failure brought on by sedative side effects in the absence of adequate monitoring [7••]. Clearly, administration of escalating doses of antiagitation medications signal a serious problem that must be aggressively evaluated. Initially, a rapid evaluation to determine or exclude the presence of disorders brought about by medical or surgical decompensations should be a priority. This is the main reason why the patient is in the ICU, attached to sophisticated monitoring devices. Emergent airway decompensations can rapidly be ruled out by capnography [8]. Acute cardiac decompensations can rapidly be detected by continuous mixed venous oximetry, and acute hypoxia by continuous pulse oximetry. Most of these devices are equipped with alarms that signal exceeded parameters before actual hemodynamic decompensation occurs. After ruling out emergent medical/surgical decompensations, the somatic effects of unrelenting agitation should be quickly and effectively blunted [9••]. This will facilitate the search for the underlying etiology without concurrent end-organ impairment.

A model for life-threatening agitation: ethanol withdrawal

Beverages that contain the short-acting central nervous system (CNS) depressant ethanol are commonly imbibed throughout the world. One might argue that most people imbibe more or less responsibly, because somewhere in their brain resides a switch that is sensitive to accumulating effects of ethanol, such as vertigo and nausea. When those effects appear, the switch is activated and a signal to stop drinking appears. There is another population of imbibers in whom such a switch is attenuated or missing, however. This population could be called 'career drinkers' and they drink continuously through the day and night, bathing their brain in a continuous flow of ethanol. This population is somewhat separate from the group referred to as 'alcoholics', whose addiction commonly presents as social problems rather than as the rote ethanol intake throughout their day. Alcoholic persons are considered to carry that diagnosis whether they drink frequently, binge drink or do not drink at all.

The CNS function of a career drinker rapidly becomes dependent on the depressive effects of ethanol, and the action of appropriate neuroreceptors are downregulated [10]. Once dependence occurs, the effect extends to other chemical CNS depressants with similar actions, such as benzodiazepines and barbiturates (cross-dependence) [11]. Tolerance to alcohol also occurs as a result of the body's ability to effectively deactivate the drug as a consequence of repeated exposure. Accordingly, higher doses of replacement cross-dependent depressants such as benzodiazepines are sometimes required to equal the various pharmacodynamic effects of alcohol (cross-tolerance) [12]. Withdrawal symptoms, manifested by the sudden decompensation of neuroreceptors, occur after the rapid ebb of CNS depressant drugs that saturate the brain, especially those that have a short duration of action (ie ethanol). Ethanol withdrawal symptoms can be ameliorated with similar, but longer acting cross-dependent CNS depressant drugs, allowing the withdrawal period to be effectively lengthened and attenuated and avoiding rapid fluctuations [13•]. CNS active drugs that achieve dependence are more potent than similar substances, however, so the process of substituting cross-dependent drugs to reset neurotransmitters does not proceed as effectively [14].

The benzodiazepines have similar side effects and complications. They tend to potentiate the analgesic effect of opiates and increase the incidence of sudden, unexpected hypotension and respiratory depression. All benzodiazepines reduce the ventilatory response to hypoxia. When given in continuous infusion, however, relatively large doses (in the order of 100–150 μg/kg) are required to produce clinically important respiratory depression [15•]. It is of the utmost importance that respiratory and hemodynamic function is monitored during the infusion of any benzodiazepine, and that the proper technology is readily available to treat sudden, unexpected decompensations. The traditional choice of house-staff for the treatment of DT, as espoused by the *Washington Manual of Medical Therapeutics* [16], has been the first-generation sedatives chlordiazepoxide and diazepam. In current practice, these drugs have been essentially superseded by second-generation sedatives that are more titratable and have fewer long-acting intermediaries. Diazepam is effective for initial control of severe symptoms, and especially for withdrawal seizures. Diazepam and chlordiazepoxide are difficult to administer in a continuous infusion, and so cannot be titrated effectively to treat the unstable and fluctuating constellation of DT symptoms effectively.

Ethanol withdrawal and delirium tremens

DT is a severe neuronal hyperexcitation syndrome that occurs following abrupt cessation of alcohol consumption [17]. Classic DT, in comparison with other related alcohol withdrawal states such as alcoholic hallucinosis and minor alcohol withdrawal, is characterized by a marked increase in motor and autonomic activity [18]. Pronounced physical dependence on alcohol and marked physical withdrawal signs (seizures, hypertension, hyperthermia, tachycardia, tachypnea) are the characteristic pathophysiologic features that indicate the severity of DT. Withdrawal symptoms result from a compensatory increase in the activity of excitatory mechanisms (upregulation) involving the neuro-

transmitters norepinephrine, dopamine, and the *N*-methyl-D-aspartate (NMDA) receptor, and diminished activity (downregulation) of the inhibitory receptors γ-aminobutyric acid (GABA)-A and α_2-adrenoceptors, after prolonged depression of the CNS by ethanol [19]. It has been hypothesized that physical withdrawal signs (tremor, hypertension, tachycardia, autonomic hyperactivity) are determined by the degree of physical dependence developed during the most recent drinking period, whereas the psychotic signs (misperceptions, hallucinations, and seizures) result from accumulated CNS hyperactivity developed over many years of repeated alcohol intoxication and withdrawal [20•]. Once developed, DT is manifested by an unpredictable, volatile and fluctuating clinical course of agitation. Because of the phenomena of cross-dependence and cross-tolerance, conventional approaches utilizing sedatives such as benzodiazepines and barbiturates may require a high dosage regimen, which can precipitate hemodynamic and ventilatory depression well before the physiologic manifestations associated with delirium can be brought under control.

Treating ethanol withdrawal: general principles

The effectiveness of treatment for DT and related states depends largely on the ability of the chosen drug to substitute for alcohol in the variety of its actions on the CNS. It has been shown [21] that the GABA-gated and glutamate-gated ion channels are the molecular sites of alcohol effect. Glutamic acid has an established role as the major excitatory amino acid neurotransmitter in the CNS, mediating fast excitatory postsynaptic potentials in the brain [22]. At least three different types of glutamate receptors have been discovered and named for the agonists that activate them: kainate, quisqualate, and NMDA. Ethanol has been shown to inhibit NMDA-activated currents in mammalian neurons over a concentration range that produces intoxication. Ethanol is thought to inhibit the NMDA-activated ion current by a novel type of interaction with a hydrophobic site that is associated with the NMDA channel. Kainate and quisqualate channels appear to be blocked only by higher alcohol concentrations that clinically produce sedation, stupor and coma in humans, suggesting that inhibition of these receptors is associated with the anesthetic properties of ethanol.

GABA is an important inhibitory neurotransmitter in the mammalian CNS. Two major types of GABA receptors (GABA-A and GABA-B) have been identified, on the basis of the selectivity of agonists/antagonists and coupling mechanisms. GABA-gated ion channels mediate presynaptic inhibition in the spinal cord and fast inhibitory postsynaptic potentials in the CNS [23]. GABA-A receptor-mediated transmission has been shown [24•] to be facilitated by alcohol, benzodiazepines, and barbiturates. Therefore, ethanol appears to have a pharmacodynamic profile similar to that of the sedative–hypnotic classes of drugs, such as benzodiazepines and barbiturates, which enhance GABAergic transmission in the mammalian CNS [25]. Chronic alcohol consumption results in upregulation of the GABA-binding sites, implicating a potential role of these changes in alcohol tolerance and withdrawal [26]. Prolonged presence of alcohol–GABA agonist in the brain appears to produce a relative 'deficiency' of GABA in the CNS that is due to the upregulation of receptors, and possibly due to the involvement of other negative feedback mechanisms.

On the other hand, downregulation of NMDA, kainate, and quisqualate receptors is most likely to induce a state of CNS hyperexcitability that involves different neuronal pools and reverberating circuits [27]. Depression and diminished function of α_2-autoadrenoreceptors have been implicated in the adrenergic hyperactivity that occurs during alcohol withdrawal [28]. Reduced level of dopamine activity has also been shown to be associated with the acute withdrawal states [29]. It has therefore been hypothesized [30] that alcoholic delirium may be directly related to the reduced level of central dopaminergic activity. Central anticholinergic properties of ethanol may contribute significantly to the psychotic and physical withdrawal signs. Physostigmine, a short-acting cholinesterase inhibitor, has been shown [31] to be effective in the prevention of development of DT. Ethanol, benzodiazepines, and barbiturates are CNS depressants, producing dose-dependent sedation and expressing cross-dependence and cross-tolerance. Based on their GABA-mimetic actions, drugs that exhibit similar pharmacodynamic profiles are benzodiazepines and barbiturates. Each of these drugs might substitute for alcohol in physically dependent individuals.

Benzodiazepines are currently the most commonly used drugs to provide prophylaxis and treatment of DT, and large doses may be required to produce anxiolysis and sedation in physically dependent patients [32]. Although benzodiazepines are efficient GABA agonists, they do not seem to cross-react with the glutamatergic system in the CNS as alcohol does. This lack of equipotency may explain the ineffectiveness of benzodiazepines in controlling agitation in DT, even when exceedingly high doses of benzodiazepines are used. Inhibition of kainate and quisqualate receptor-mediated responses have been implicated in the general anesthetic properties of ethanol, and have also been observed in barbiturates [33]. Because of this additional reaction with glutamate receptor mechanisms, barbiturates appear to be closer to the neurochemical effects of alcohol than are benzodiazepines, but exhibit more clinical side effects.

Treating delirium tremens: sedative therapy

The general approach to the treatment of physical drug dependency is the substitution of the drug that has been

abused with another one that has a similar pharmacologic profile. Following such a substitution of a cross-dependent substance, weaning (resetting neurotransmission) proceeds in a more predictable and titrated manner [34]. The effective treatment of ethanol withdrawal depends greatly on when the symptoms are recognized for what they are. It is not uncommon for career drinkers to fool family and friends into believing they are merely 'social drinkers'. The difference is that they drink socially 18 h a day. Thus, when they fall and break their hip and land in a hospital, there may not be a history of serious drinking. When the patient begins to exhibit withdrawal symptoms, it may be misdiagnosed for a fairly long period of time, during which the symptomatology may inexorably proceed to the 'storm phase'. The first course of action should be the administration of a cross-dependent sedative, in doses that are titrated to achieve control of the patient with a minimum of obfuscating side effects. As the severity of the disease progresses, rapid changes in restlessness necessitate the choice of a drug with a rapid titratability, adjusting levels of sedation to the prevalent state of CNS excitation.

There is little current rationale for the use of chlordiazepoxide or diazepam in the treatment of ethanol withdrawal. They each have a number of long-acting intermediaries, they cannot be reliably given intravenously, and they cannot be used in a continuous infusion and so cannot be titrated effectively to the unstable and fluctuating constellation of DT symptoms.

Lorazepam is an intermediate to long-acting benzodiazepine with typical anxiolytic and sedative qualities [35]. The drug has a mild amnestic effect as well. Lorazepam 4 mg is about equivalent to 10 mg diazepam [36]. Intermediary products do not accumulate and metabolism does not require hepatic oxidative metabolism; it only requires glucuronidation, which makes it an attractive drug in liver insufficiency. Lorazepam has been approved for oral, intramuscular, and intravenous use, and the traditional dose for patients in the ICU has been 1–2 mg every 3–4 h.

Midazolam is a short-acting CNS depressant. Midazolam is relatively water soluble compared with other benzodiazepines, increasing the rapidity of its action [37]. The potency of midazolam is about three to four times that of diazepam, and it has a shorter elimination half-life of 1.5–3.5 h. Sedation after intravenous injection is achieved within 1–5 min, with a duration of action of less than 2 h [38]. The treatment for noradrenergic-induced panic and anxiety differs radically from that of similar symptoms induced by heart failure. Midazolam is uniquely practical in the ICU environment because its rapid-acting/short duration properties allow its use as a continuous titrated infusion [39]. This makes midazolam useful for titrated sedation, anxiolysis, and anterograde amnesia in the conscious, restless patient with unstable hemodynamics. There is a relatively wide margin of safety when midazolam is administered by continuous infusion in the ICU setting, where facilities are available for appropriate monitoring [40].

Psychoactive drugs in the major tranquilizer class may aggravate alcohol withdrawal states by several mechanisms. First, phenothiazines have been shown to enhance norepinephrine release from the cerebral cortex of experimental animals, and to antagonize the action of clonidine on α_2-autoreceptors. Second, there is a possibility of triggering the malignant neuroleptic syndrome in predisposed hyperthermic patients. Third, several well-controlled trials have clearly documented an aggravating effect of neuroleptics on physical withdrawal signs, precipitating seizures and increasing mortality rate [41]. Therefore, on the basis of existing evidence suggesting detrimental effects in different phases of alcohol withdrawal states, major tranquilizers should be excluded from the treatment of DT. It should, however, be noted that there are references that suggest that neuroleptics can be useful in low doses, especially in combination with benzodiazepines for lower levels of DT [42].

Neuroleptic butryphenones such as haloperidol seem to be beneficial in the treatment of restlessness and aggressive agitation by reordering dopamine neurotransmission, especially in combination with benzodiazepines [43]. Haloperidol appears to exert a diffuse depressive effect at the subcortical, mid-brain and brainstem reticular formation levels. The precise antipsychotic mechanism is not known. The drug may also inhibit catecholamine receptors and reuptake of various neurotransmitters in the mid-brain. Haloperidol produces less sedation than phenothiazines, with very little effect on heart rate, blood pressure, and respiration [44•]. A unique effect of haloperidol is a relatively strong suppression of spontaneous musculoskeletal hyperactivity and behavior that results from hyperdopaminergic brain function, without pronounced sedation or hypotension. There appears to be a rather narrow range between therapeutic doses for antipsychosis and the dose that precipitates extrapyramidal reactions. Currently, intravenous dosage is not 'approved' by the US Food and Drug Administration, but the drug is commonly given by this mode, and there has been a broad range of experience with it in the peer-reviewed medical literature [45•,46•]. The dose and frequency of administration is dependent on the degree of agitation and, to a lesser extent, on the patient's age.

Adverse hemodynamic effects from neuroleptics are rare in healthy individuals [47,48]. Combined use of lorazepam and haloperidol has been reported to be most effective in combining antipsychotic effects and sedation, with a minimum of side effects [49]. Haloperidol may be safer to use in alcohol-related delirium than was previously thought [50]. One study [51] showed that haloperidol did not precipitate any untoward side effects when used to treat a hetero-

genous population of patients with head injuries, including 90 acutely alcohol-intoxicated patients. Tardive dystonia, oculogyric crisis, torticollis, and trismus all occur rarely and are mostly dose related. Neuroleptic malignant syndrome may occur with any dose of haloperidol administration, requiring ICU admission and aggressive, titrated life support.

Adjuvants to benzodiazepine sedation: clonidine

In addition to its α-blockade actions, clonidine is an anxiolytic drug [52]. Clonidine is thought to act by competitively binding opiate and catecholaminergic autoreceptors, decreasing the amount of opiates required to achieve the same sedative effect [53]. As a consequence, respiratory depression, hypotension, and other side effects of narcotic sedatives are significantly attenuated, especially in hemodynamically unstable patients. Clonidine is almost completely absorbed after oral administration, but takes 60–90 min to reach peak plasma concentration. Drug delivery through a transdermal patch takes much longer to achieve effective blood levels, and a minimum of 2 days to achieve a steady-state concentration [54]. Transdermal clonidine has been favorably compared with chlordiazepoxide in a double-blind randomized clinical trial of the treatment of ethanol withdrawal [55]. Unfortunately, clonidine is not yet approved for intravenous use in the USA, but intravenous administration is common in Europe and elsewhere [56].

Fentanyl: increasing benzodiazepine potency

Fentanyl is a synthetic opioid with morphine-like activity. Fentanyl has a rapid onset of analgesic action (2–4 min), short duration (30–40 min), and an often under-appreciated sedative action as well [57]. Addition of the short-acting analgesic fentanyl adds analgesia to the anxiolytic action of midazolam, retains real-time titration ability for about 48 h, and increases the clinical potency of both drugs [58]. Fentanyl promotes less histamine release and has significantly less effect on cardiac dynamics than morphine. Fentanyl adds an accurately titratable analgesic and sympatholytic effect to the anxiolytic effects of benzodiazepines, and is most effectively used in the continuous infusion mode, because of its brief span of action [59]. The administration of fentanyl plus a benzodiazepine has the potential to produce unexpected hypotension and respiratory depression [60]. Occasionally, the rapid administration of high doses of fentanyl has resulted in muscular and glotic rigidity during the induction of anesthesia. This complication is reversible with naloxone [61]. Close hemodynamic and ventilatory monitoring is indicated due to the augmented potency of this combination.

Flumazenil: titrating sedation at the level of neurotransmission

The administration of sedatives complicates the management of ICU patients when the extent or duration of sedation prevents assessments that require lucidity and therapies that require patient cooperation. Examples include the performance of neurologic examinations and the measurement of effort-dependent weaning parameters in patients undergoing mechanical ventilation. Moreover, patients who are sedated for prolonged periods tend to develop sedative accumulation throughout the various body water compartments, leading to protracted lassitude once drugs are removed from active infusion. Patients who are sedated for prolonged periods suffer increased risk for complications from immobility, such as deep venous thrombosis, decubitus skin ulceration, and pressure-induced peripheral neuropathy. It seems desirable to keep patients sedated for the minimum time needed. The ability to reverse sedation rapidly when it interferes with patient care, or is no longer required, could improve the management of a sizeable subgroup of ICU patients.

Flumazenil is an imidazobenzodiazepine that antagonizes the effects of benzodiazepine agonists by competitive interaction at the cerebral benzodiazepine receptor site [62]. It does not antagonize the effects of other drugs that do not affect benzodiazepine receptors, such as narcotics, barbiturates, cyclic antidepressants, and ethanol. Because benzodiazepines are frequently utilized for prolonged sedation in ICUs, flumazenil may be useful for the titrated reversal of sedation in this environment [63]. The recommended initial dose of flumazenil, for the reversal of the sedative effects of benzodiazepines administered for conscious sedation or general anesthesia, is 0.2 mg administered over 15 s [64]. It is important to remember, however, that benzodiazepine effect can easily be reversed in a smooth and titrated manner with a low-dose continuous infusion of flumazenil, starting at 0.05 mg/h and with constant bedside observation of the effect [65•]. Slow and progressive lightening up occurs, followed by progressive resumption of quietude when the infusion is stopped. Since it is a smooth transitional effect, 'sudden awakening' complications do not occur. Continuous infusion of flumazenil may be efficacious for titrating the effect of sedation at the level of their CNS receptor site, allowing the practitioner further options for accurate control of sedative agents.

Routes of drug administration

Oral administration of sedatives is problematic for agitated patients because of erratic absorbtion and the complications that are inherent in placing nasogastric tubes for drug administration. Intramuscular absorption of drugs is influenced by the ratio of ionized to un-ionized drug, site of injection, blood flow to the region, and amount of drug metabolized before entry into the systemic circulation. All of these variables are affected by critical illness. Intramuscular injection usually requires musculoskeletal activity and adequate tissue perfusion to enhance absorption into the systemic circulation. Because patients in the ICU gener-

ally lie still, they tend to absorb drugs from the muscles erratically. ICU patients also frequently suffer from decreased tissue perfusion because of varying degrees of heart failure and multiorgan insufficiency, as well as the decreasing reliability of muscular absorption.

Intravenous administration of sedatives offers the advantage of rapid onset and potent end-organ effect, very big pluses in the treatment of unstable patients. Insertion of a central venous catheter is usually indicated to ensure that the drug continues to access the central circulation, as peripheral intravenous infusions may infiltrate with very little warning, particularly in the middle of the night. Intra-arterial catheters are indicated for constant blood pressure monitoring and easy access for blood sampling. Most rapidly acting drugs are very lipid soluble and can only be titrated by intravenous administration. The effective titratability of these drugs decreases with time, however, as the volume of distribution throughout the body water compartments increases. Organ insufficiency, particularly liver failure, also decreases the short-term titratability of most sedatives by prolonging the serum half-life.

Continuous infusions of analgesics and sedatives are a very effective method for avoiding the bolus medication therapies that initiate a 'peak' of therapeutic action followed by a variable 'valley' period, during which the patient receives little or no drug effect. Current literature suggests that high-risk cardiac patients are jeopardized by relatively brief periods of ineffective analgesia [66]. Intermittent periods of sympathetic stimulation due to ineffective analgesia and sedation can cause relatively profound deleterious effects on compromised myocardium [67]. Continuous intravenous infusions of short-acting agents such as midazolam, propofol, and fentanyl allow titration of plasma level effects to a fluctuating baseline of pain, anxiety, and discomfort. This real-time titration of natural fluctuations may occur with minimum hemodynamic and respiratory suppression. Increased costs of newer short-acting agents are justified if complications are avoided as patients achieve more effective analgesia and sedation, avoiding the blanket effects of less selective regimens.

Ethanol infusions

Although there is a paucity of evidence in the literature to support it, intravenous 10% ethanol infusions have been used for treating DT. On one level, this treatment is effective because it directly replaces the substance that is withdrawn from the patient, resetting brain receptors with equal potency. On other levels, however, this treatment regimen is problematic. There is some evidence that patients whose brain function is re-regulated with cross-dependent substances such as benzodiazepines have a stronger potential to choose sobriety after the detoxification process. This is because the cross-dependent drugs are not as euphoric and therefore less addictive than ethanol. They become dependent on a more benign drug that is easier to rehabilitate from. Ethanol is also a very toxic drug to all organ systems, exacerbating gastric bleeds, pancreatitis, and liver failure. There is no evidence in the literature that ethanol infusions are any more effective than a thoughtful detoxification process using cross-dependent sedatives in a carefully titrated care plan.

The 'storm phase' of delirium tremens

When the diagnosis is delayed for a considerable period and the 'storm phase' is entered, it can be very difficult to deal with DT because of cross-tolerance to cross-dependent drugs such as benzodiazepines. Rapid changes from restlessness to somnolesence necessitate the choice of a drug with a rapid titratability, adjusting levels of sedation to the prevalent state of CNS excitation. Propofol, a sedative–anesthetic agent with a rapid onset and short duration of action, appears to have a superior neuropharmacodynamic profile in replacing actions of alcohol and alleviating the withdrawal symptomatology than barbiturates and benzodiazepines, making it attractive as a substitute treatment. Although the neuropharmacologic mechanism of action of propofol has not yet been elucidated completely, there is evidence suggesting that propofol may potentiate GABA-evoked responses and may activate the GABA-A receptors [68]. GABA-mediated presynaptic and postsynaptic inhibition is believed to be related to the direct interaction of propofol with the GABA receptor complex [69].

Propofol appears to produce its inhibitory activity at both spinal and supraspinal neuronal synapses [70]. It brings about a dose-dependent diminution of cerebral blood flow, decreases global cerebral metabolic rate, and is potent enough to create a flat electroencephalogram in high doses [71]. This state is rapidly reversible with no neurologic change thereafter, which suggests that propofol may provide cerebral protection. Potent general depressant and anesthetic actions of propofol provide the basis for the assumption that it produces these effects, through its counteraction not only with GABA, but also with the glutamate-gated ion channels. Therefore, the pharmocodynamic profile of propofol appears to be superior to that of the benzodiazepines, approaching that of ethanol, which makes it very advantageous in treatment of the severe ethanol withdrawal states.

Propofol is a diisopropilphenol and is chemically related to alcohols. Therefore, being an aromatic sedative–hypnotic alcohol, it is believed to exhibit wider cross-dependence with the neuropharmocodynamic profile of alcohol than do conventional benzodiazepines or barbiturates. At the same time, propofol appears to have different pharmacokinetics and reduced cross-tolerance due to its predominant glucuronidation and excretion in the bile. This may allow propofol to exert a more dramatic alleviating effect on withdrawal symptomatology than benzodiazepines, which

show a narrower spectrum of neuropharmacodynamic effects. Propofol produces a progressive, dose-dependent continuum of anxiolysis, hypnosis, sedation, and, finally, anesthesia, which can be maintained by a rapidly adjustable, titrated infusion. Propofol was compared with midazolam with regard to its quality as a sedative agent, and was found to be superior because of the significantly shorter recovery time, improved titration during sedation, reduced posthypnotic sleep, and faster weaning from mechanical ventilation [72]. The lack of accumulation allows the drug to be given by prolonged infusion. Some clinical and experimental studies in which propofol has been used for sedation and anesthesia [73] have revealed cardiovascular depression. This phenomenon is believed to be associated with both a mild negative inotropic effect and a decrease in systemic vascular resistance, and is especially evident in patients with hypovolemia and compromised cardiovascular status [74].

Delirium tremens and catecholamine storm

One of the therapeutic goals in the treatment of DT is to avoid hemodynamic decompensation resulting from the end-organ effect of catecholamine storm. Recent studies suggest that decreasing stress-related tachycardia by the use of super-selective, ultra-short-acting β-adrenergic blocking agents may result in an aggregate benefit to hemodynamics in heart failure by improving cardiac function by proportionally more than the small amount of negative inotropy inherent to the drug. The short duration and rapid titratability of the short-acting β-adrenergic antagonist esmolol has been found to be advantageous to older, longer-acting drugs in decreasing the adverse affects of excessive tachycardia, increasing coronary artery blood flow during diastole, and decreasing myocardial oxygen consumption.

Several intravenous β-adrenergic antagonists are available for use in the ICU. Atenolol is relatively water soluble, incompletely absorbed, and cleared by the renal route, and has a fairly long half-life [75]. Metoprolol is highly lipid soluble, more completely absorbed, and cleared by the hepatic route, and has a relatively short half-life [76]. Esmolol, a short-acting, rapidly titratable β-adrenergic blocking agent has been demonstrated [77,78] to manifest a preferentially negative chronotropic effect and can be titrated by continuous infusion. The effects of hypertension with concomitant tachycardia can be safely resolved using titrated intravenous infusions of labetalol, a drug that manifests both α-adrenergic and β-adrenergic antagonistic properties [79]. Labetalol can also be utilized in a continuous infusion, titrated in relatively brief intervals.

Cardiac function and fluid volume status can be accurately monitored by pulmonary artery catheter and continuous mixed venous oximetry, free from variations induced by patient movement. Once the agitation syndrome runs its course, hemodynamic and cerebral parameters will begin to normalize, and therapy can be deintensified safely.

Delirium tremens: an acute intensive care unit emergency

Escalating dosages of sedatives in the face of increasing agitation is a genuine medical emergency that must be dealt with aggressively. Therapeutic musculoskeletal paralysis is frequently considered when the deleterious side effects of sedation begin to pose a hemodynamic or respiratory risk, and the patient's neurobehavioral status is still not controlled [80]. Hemodynamic deterioration from the effects of agitation can precipitate angina, heart failure, and cardiac arrhythmias by increasing myocardial work and oxygen consumption in the face of a fixed coronary artery output. If the severely agitated patient becomes hypoxic and hypercapnic as a direct result of the effects of agitation, therapeutic paralysis, intubation, and mechanical ventilation will be necessary to reverse deleterious end-organ effects [81]. Intentional therapeutic paralysis may be complete or attenuated, allowing the patient some movement but not unrestrained activity. Doses of neuromuscular relaxants may effectively be guided by peripheral nerve stimulators according to protocol [82].

Suspended animation using musculoskeletal paralytic agents will effectively stop increased oxygen consumption and the effects of muscular hyperactivity on end organs. It must be remembered, however, that underneath paralysis lies a disordered cerebral function that is vulnerable to damage from catecholamine storm and hemodynamic instability. In the past, sedation has been titrated under paralysis until tachycardia and hypertension normalize, suggesting that patient comfort has been achieved. This is a rough way of determining patient comfort under the effects of paralysis, but the advent of cerebral function monitoring has improved on this technique. To ensure that the patient does not suffer a 'buried alive' sensation under paralysis, it is highly preferable that sedation is tailored to some objective assessment of real brain activity.

Once the patient is placed in suspended animation, many end organs can be protected while specific therapeutics or merely 'tincture of time' resolves the fundamental etiologies of the agitation syndrome. Adverse effects of exogenous catecholamines and endogenous neurotransmitters on the brain can be blunted by titrating sedative, hypnotic, and analgesic drugs to levels of cerebral electrical activity, as monitored by cerebral function monitors in real-time. Catecholamine storm and severe tachycardia causes a dramatic increase in myocardial oxygen consumption, which can lead to severe cardiac and hemodynamic complications.

Conclusion

Ethanol withdrawal was in the past considered a psychiatric disease. Detoxification was accomplished using

straitjackets, rubber rooms, and leather restraints. Today, we recognize it as a potentially lethal process that requires closely titrated care in a highly monitored setting, in which normal and abnormal physiology can be appropriately manipulated to the best interests of the patient. The aim of short-term detoxification by the path of least resistance followed by quick discharge, anticipating that the patient will immediately resume drinking, is not realistic in a world in which long-term goals are realistically attainable. 'Detoxification' in a titrated manner in the ICU by establishing cross-dependence puts patients in a position where they are no longer as addicted to a euphoric yet toxic drug, and eventual rehabilitation is thereby facilitated. This seems like a noble and attainable goal for ICU care. Effective treatment of 'severe' symptomatology requires aggressive management. An indication to begin thinking about aggressive treatment of cardiodynamics is the rapid escalation of symptoms in the face of increasing sedation. When sedation alone is insufficient, medication that is formulated to lessen the effect of CNS sympathetic discharge on end organs must be applied.

References

Articles of particular interest have been highlighted as:
- • of special interest
- •• of outstanding interest

1. Lipowski ZJ: *Delirium: Acute Brain Failure in Man*. Springfield, Ill: Charles C Thomas Publishers, 1980:152–197.
• This very comprehensive text covers the psychologic and physiologic manifestations of delirium.

2. Kehlet H: **Pain relief and modification of the stress response.** In: *Acute Pain Management*. Cousins MJ, Phillips GD (editors). New York: Churchill Livingstone, 1986:46.

3. Crippen DW, Ermakov S: **Stress, agitation and brain failure in critical care medicine.** *Crit Care Nursing Quart* 1992, **15**:52–74.

4. Crippen DW. **Pharmacologic treatment of brain failure and delirium.** *Crit Care Clin* 1994, **10**:733–765.

5. Easton C, MacKenzie F: **Sensory-perceptual alterations: delirium in the intensive care unit.** *Heart Lung* 1988, **17**:229–237.
• An extensive description of delirium from the ICU patient's point of view is presented.

6. Freemon FR: *Organic Mental Disease*. Jamaica, New York: SP Medical and Scientific Books, 1981:81–94.
•

7. Crippen DW: **Neurologic monitoring in the intensive care unit.** *New Horizons* 1994, **2**:107–120.
•• A discussion is provided of brain function monitoring in the ICU. DT as a life-threatening agitation syndrome and the role of bedside compressed spectral array monitoring are discussed.

8. Wright SW: **Conscious sedation in the emergency department: the value of capnography and pulse oximetry.** *Ann Emerg Med* 1992, **21**:551–555.

9. Mangano DT, Siliciano D, Hollenberg M, *et al*. **Postoperative myocardial ischemia.** *Anesthesiology* 1992, **76**:342–353.
•• Strong evidence is provided that agitation syndromes have the capability to precipitate hemodynamic deterioration as oxygen consumption exceeds oxygen transport. The suggestion is made that outcome is adversely affected.

10. Collins GB: **Contemporary issues in the treatment of alcohol dependence.** *Psychiatr Clin North Am* 1993, **16**:33–48.

11. Newman LM, Curran MA, Becker GL: **Effects of alcohol intake on anesthetic responses to diazepam and thiopental in rats.** *Anesthesiology* 1986, **65**:196–200.

12. Ticku MK: **Ethanol interaction at the γ-aminobutyric acid receptor complex.** *Ann NY Acad Sci* 1991, **625**:136–144.

13. Benzer DG: **Quantification of the alcohol withdrawal syndrome in 487 alcoholic patients.** *J Subst Abuse Treat* 1990, **7**:117–123.
• This is a categoric description of the objective features of ethanol withdrawal in a large array of patients.

14. Fassoulaki A, Farinotti R, Servin F, *et al*: **Chronic alcoholism increases the induction dose of propofol in humans.** *Anesth Analg* 1993, **77**:553–556.

15. Lineaweaver WC, Anderson K, Hing DN: **Massive doses of midazolam infusion for delirium tremens without respiratory depression.** *Crit Care Med* 1988, **16**:294–295.
• The suggestion is made that larger benzodiazepine doses than those that usually cause respiratory depression are not as obtunding when used in ethanol withdrawal patients.

16. Ewald GA, McKenszie CR (editors): *Washington Manual of Medical Therapeutics*. 534–535.

17. Newman LM, Curran MA, Becker GL: **Effects of chronic alcohol intake on anesthetic responses to diazepam and thiopental in rats.** *Anesthesiology* 1986, **65**:196–200.

18. Collins GB: **Contemporary issues in the treatment of alcohol dependence.** *Psychiatr Clin North Am* 1993, **16**:33–48.

19. Collingridge GL, Lester RAJ: **Excitatory amino acid receptors in the vertebrate central nervous system.** *Pharmacol Rev* 1989, **41**:143–210.

20. Crippen D, Ermakov S: **Titrated treatment of delirium tremens using continuous propofol infusion.** *St Francis Journal of Medicine (online)*: http://www.sfhs.edu/journal/v.2_n.1/clinical/clinical.htm
• Continuous propofol infusion is described in the treatment of life-threatening ethanol withdrawal, with few adverse side effects.

21. Ticku MK: **Ethanol interaction at the gamma-aminobutiric acid receptor complex.** *Ann NY Acad Sci* 1991, **625**:136–144.

22. Tsai G, Gastfriend DR, Coyle JT: **The glutamatergic basis of human alcoholism.** *Am J Psychiatry* 1995, **152**:332–340.

23. Skolnick P, Paul SM: **The benzodiazepine/GABA receptor chloride channel complex.** In: *ISI Atlas of Science: Pharmacology*, vol 2. Philadelphia: Institute for Scientific Information, 1988:19–22.

24. Gillman MA, Lichtigfeld FJ: **Receptor hypothesis of the alcohol withdrawal state.** In: *CNS Receptors from Molecular Biology to Behaviour*. Edited by Mandel P, De Feudis FV. New York: Raven Press, 1983:405–415.
•

25. Weight FF, Aguayo LG, White G, *et al*: **GABA- and glutamate-gated ion channels as molecular sites of alcohol and anesthetic action.** *Adv Biochem Psychopharmacol* 1992, **47**:335–347.

26. Cancas A, Santoro G, Mascia MP, *et al*: **The action of the general anesthetic propofol on GABA-A receptors.** *Adv Biochem Psychopharmcol* 1992, **47**:349–363.

27. Daniels S, Zhao DM, Inman N: **Effects of general anesthetics and pressure on mammalian excitatory receptors expressed in *Xenopus* oocytes.** *Ann NY Acad Sci* 1991, **625**:108–115.

28. Romano J, Engel GL: **Physiologic and psychologic considerations of delirium.** *Med Clin North Am* 1944, **28**:629–638.

29. Wozniak KM, Pert A, Linnoila M: **Antagonism of 5-HT3 receptors attenuates the effects of ethanol on extracellular dopamine.** *Eur J Pharmacol* 1990, **187**:287–289.

30. McMicken DB: **Alcohol withdrawal syndromes.** *Emerg Med Clin North Am* 1990, **8**:805–819.

31. Schneck HJ, Rupreht J: **Central anticholinergic syndrome in anesthesia and intensive care.** *Acta Anesthesiol Belg* 1989, **40**:219–227.

32. Gurthrie SK: **The treatment of alcohol withdrawal.** *Pharmacotherapy* 1989, **9**:131–143.

33. Willow M, Johnston GAR: **Pharmacology of barbiturates: electrophysiological and neurochemical studies.** *Int Rev Neurobiol* 1983, **24**:15–49.

34. Hollister LE: **Interactions between alcohol and benzodiazepines.** *Recent Dev Alcohol* 1990, **8**:233–239.

35. Deppe SA, Sipperly ME, Sargent AI, Kuwik RJ, Thompson DR: **Intravenous lorazepam as an amnestic and anxiolytic agent in the intensive care unit: a prospective study.** *Crit Care Med* 1994, **22**: 1248–1252.

36. Greenblatt DJ, Ehrenberg BL, Gunderman J, *et al*: **Kinetic and dynamic study of intravenous lorazepam: comparison with intravenous diazepam.** *J Pharmacol Exp Ther* 1989, **250**:134–140.

37. Westphal LM, Cheng EY, White PF, *et al*: **Use of midazolam infusion for sedation following cardiac surgery.** *Anesthesiology* 1987, **67**:257–262.

38. Driessen JJ, Dirksen MSC, Rutten JMJ, *et al*: **Continuous infusion of midazolam during anaesthesia and postoperative sedation after maxillofacial surgery.** *Acta Anaesthesiol Scand* 1989, **33**:116–121.

39. Milgrom P, Weinstein P, Fiset L, *et al*: **The anxiolytic effects of intravenous sedation using midazolam alone or in multiple drug techniques.** *J Oral Maxillofacial Surg* 1994, **52**:219–224; discussion:225.

40. Berggren L, Erikson I, Mollenholt P, *et al*: **Changes in respiratory pattern after repeated doses of diazepam and midazolam in healthy subjects.** *Acta Anaesthesiol Scand* 1987, **31**:667–672.

41. Glenthoj B, Hemmingsen R, Barry DI, *et al*: **Electrical kindling of rats treated discontinuously or continuously with haloperidol.** *Eur J Pharmacol* 1993, **236**:401–409.

42. Spies CD, Dubisz N, Neumann T, Blum S, Muller C, *et al*: **Therapy of alcohol withdrawal syndrome in intensive care unit patients following trauma: results of a prospective, randomized trial.** *Crit Care Med* 1996, **24**:414–422.

43. Ayd FJ: **Intravenous haloperidol-lorazepam therapy for delirium.** *Int Drug Ther Newslett* 1984, **19**:33–35.

44. Clinton JE, Sterner S, Stelmachers Z, *et al*: **Haloperidol for sedation**
• **of disruptive emergency patients.** *Ann Emerg Med* 1987, **16**:319–322.
This paper suggests that intravenous haloperidol is effective for a widely heterogeneous population of agitated patients, with few side effects.

45. Tesar GE, Murray GB, Cassem NH: **Use of high-dose intravenous**
• **haloperidol in the treatment of agitated cardiac patients.** *J Clin Psychopharmacol* 1985, **5**:344–347.
This paper suggests that very high doses of haloperidol are sometimes needed to control the severely agitated patient, with few untoward side effects.

46. Riker RR, Fraser GL, Cox PM: **Continuous infusion of haloperidol**
• **controls agitation in critically ill patients.** *Crit Care Med* 1994, **22**:433–440.
This paper suggests that continuous infusion of haloperidol is safe and effective for the treatment of delirium in the monitored environment.

47. Sharma ND, Rosman HS, Padhi D, Tisdale JE: **Torsades de pointes associated with intravenous haloperidol in critically ill patients.** *Am J Cardiol* 1998, **81**:238–240.

48. Iwahashi K, Nakamura K, Miyatake R, Suwaki H, Hosckawa K: **Cardiac effects of haloperidol and carbamazepine treatment.** *Am J Psychiatry* 1996; **153**:135.

49. Menza MA, Murray GB, Homes VF, *et al*: **Controlled study of extrapyramidal reactions in the management of delirious, medically ill patients: intravenous haloperidol versus intravenous haloperidol plus benzodiazepines.** *Heart Lung* 1988, **17**:238–241.

50. Spies CD, Dubisz N, Funk W, *et al*: **Prophylaxis of alcohol withdrawal syndrome in alcohol-dependent patients admitted to the intensive care unit after tumour resection.** *Br J Anaesth* 1995, **75**:734–739.

51. Clinton JE, Sterner S, Stelmachers Z, Ruiz E: **Haloperidol for sedation of disruptive emergency patients.** Ann Emerg Med 1987, **16**:319–322.

52. Bohrer H, Bach A, Layer M, *et al*: **Clonidine as a sedative adjunct in intensive care.** *Intens Care Med* 1990, **16**:265–266.

53. Scheinin M, Schwinn DA: **Site of hypnotic actions of α2-adrenoceptor agonists?** *Anesthesiology* 1992, **76**:873–875.

54. Toon S, Hopkins KJ, Aarons L, Rowland M: **Rate and extent of absorption of clonidine from a transdermal therapeutic system.** *J Pharm Pharmacol* 1989, **41**:17–21.

55. Baumgartner GR, Rowen RC: **Transdermal clonidine versus chlordiazepoxide in alcohol withdrawal: a randomized, controlled clinical trial.** *South Med J* 1991, **84**:312–321.

56. Bernard JM, Hommeril JL, Passuti N, Pinaud M: **Postoperative analgesia by intravenous clonidine.** *Anesthesiology* 1991, **75**:577–582.

57. Katz R, Kelly HW: **Pharmacokinetics of continuous infusions of fentanyl in critically ill children.** *Crit Care Med* 1993, **21**:995–1000.

58. Milgrom P, Beirne OR, Fiset L, *et al*: **The safety and efficacy of outpatient midazolam intravenous sedation for oral surgery with and without fentanyl.** *Anesthesia Prog* 1993, **40**:57–62.

59. Lenz KL, Dunlap DS: **Continuous fentanyl infusion: use in severe cancer pain.** *Ann Pharacother* 1998, **32**:316–319.

60. Bergman I, Steeves M, Burchart G, Thompson A: **Reversible neurologic abnormalities associated with prolonged intravenous midazolam and fentanyl administration.** *J Pediatr* 1991, **119**:644–649.

61. Klausner JM, Caspi J, Lelcuk S, *et al*: **Delayed muscular rigidity and respiratory depression following fentanyl anesthesia.** *Arch Surg* 1988, **123**:66–67.

62. Skielboe M, Andersen PM, Weber M, *et al*: **Reversal of benzodiazepine intoxication by flumazenil.** *Resuscitation* 1991, **22**:245–252.

63. Yoshino A, Nishimura K, Tatsumi K, *et al*: **Effect of continuous infusoin of flumazenil on unexpected post operative resedatin by midazolam.** *Masui* 1994, **43**:1668–1674.

64. Weinbroum A, Rudick V, Sorkine P, *et al*: **Use of flumazenil in the treatment of drug overdose: a double-blind and open clinical study in 110 patients.** *Crit Care Med* 1996, **24**:199–206.

65. Park GR, Bodenham A: **Flumazenil infusion or repeated doses**
• **[letter].** *Anaesthesia* 1989, **44**:365.
This paper suggests that continuous infusion of flumazenil is safe and effective for the titrated reversal of the sedative effects of benzodiazepines.

66. Barvais L, Dejonckheere M, Dernovoi B, *et al*: **Continuous infusion of midazolam or bolus of diazepam for postoperative sedation in cardiac surgical patients.** *Acta Anaesthesiol Belg* 1988, **39**:239–245.

67. Hall RI, Maclaren C, Smith MS, *et al*: **Light versus heavy sedation after cardiac surgery: myocardial ischemia and the stress response.** *Anesth Analg* 1997, **85**:971–978.

68. Hales T, Lambert JJ: **The actions of propofol on inhibitory amino acid receptors of bovine adrenomedullary chromaffin cells and rodent central neurones.** *Br J Pharmacol* 1991, **104**:619–628.

69. Peduto VA, Concas A, Santoro G, *et al*: **Biochemical and electrophysiologic evidence that propofol enhances GABAergic transmission in the rat brain.** *Anesthesiology* 1991, **75**:1000–1009.

70. Aitkenhead AR, Willatts SM, Park GR, *et al*: **Comparison of propofol and midazolam for sedation in critically ill patients.** *Lancet* 1989, **ii**:704–709.

71. Spencer EM, Green JL, Willattis SM: **Continuous monitoring of depth of sedation by EEG spectral analysis in patients requiring mechanical ventilation.** *Br J Anaesth* 1994, **73**:649–654.

72. McMurray TJ, Collier PS, Carson IW, *et al*: **Propofol for sedation after open heart surgery. A clinical and pharmacokinetic study.** *Br J Anaesth* 1990, **2**:322–327.

73. Stephan H, Sonntag H, Schenk HD, *et al*: **Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease.** *Br J Anesthesia* 1986, **58**:969–975.

74. Larsen R, Rathgeber J, Bagdahn A: **Effects of propofol on cardiovascular dynamics and coronary blood flow in geriatric patients. A comparison with etomidate.** *Anesthesia* 1988; 43:25–31.

75. Newton GE, Azevedo ER, Parker JD: **Inotropic and sympathetic responses to the intracoronary infusion of a beta2-receptor agonist: a human in vivo study.** *Circulation* 1999, **11**:2402–2407.

76. Goldstein S, Kennedy HL, Hall C, Anderson JL: **Metoprolol CR/XL in patients with heart failure: A pilot study examining the tolerability, safety, and effect on left ventricular ejection fraction.** *Am Heart J* 1999, **138**:1158–1165.

77. Sung RJ, Blanski L, Kirshenbaum J: **Clinical experience with esmolol, a short acting beta adrenergic blocker in cardiac arrhythmias and myocardial ischemia.** *J Clin Pharmacol* 1986, **26(Suppl A)**:A15–A26.

78. Kirshenbaum JM, Kloner A, Elliott M, *et al*: **Use of an ultrashort acting beta blocker with acute myocardial ischemia: hemodynamic and electrical consequences.** *Am J Cardiol* 1985 **12**:773–780.

79. van Zwieten PA: **An overview of the pharmacodynamic properties and therapeutic potential of combined alpha- and beta-adrenoceptor antagonists.** *Drugs* 1993, **45**:509–517.

80. Weddington WW Jr: **The mortality of delirium: an underappreciated problem?** *Psychosomatics* 1982, **23**:1232–1235.

81. Blachly PH, Kloster FE: **Relation of cardiac output to postcardiotomy delirium.** *J Thorac Cardiovasc Surg* 1966, **52**:422–427.

82. Bevan DR: **Monitoring and reversal of neuromuscular block.** *Am J Health Syst Pharmacol* 1999, **56(Suppl 1)**:S10–S13.

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