EDITORIAL

Baclofen to Prevent Agitation Caused by Alcohol Withdrawal in the ICU

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Alcohol use and abuse is common in many societies and is associated with adverse effects on health. According to the US National Institute on Alcohol Abuse and Alcoholism, in 2019, an estimated 14.1 million adults aged 18 years and older had alcohol use disorder, defined as "chronic relapsing brain disease characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences."[1] Among the numerous alcohol-related diseases and harms, including liver cirrhosis, obesity, some cancers, injury, and suicide, only some directly contribute to acute critical illness. However, among patients with alcohol use or abuse who require intensive care unit (ICU) or hospital admission, alcohol withdrawal is an important factor that may complicate treatment and increase the risk of adverse outcomes.

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Alcohol activates γ-aminobutyric acid type A ($GABA_A$) receptors, initially suppressing inhibitory neurotransmitter systems (relaxing social inhibitions) and, at higher levels, reducing consciousness. Chronic use induces tolerance by downregulating $GABA_A$ receptors. Abrupt abstinence induces a hyperexcitable state within 6 to 24 hours, characterized by anxiety, agitation, sympathetic activity, and hallucinations and seizures in severe cases. Alcohol withdrawal, rather than alcohol use per se, is the more common reason for alcohol-related issues among patients admitted to the ICU. A systematic review from 2013 found that the prevalence of alcohol withdrawal syndrome (AWS) in general ICU populations ranged from 0.5% to 8%, but was up to 52% among patients with alcohol-related admissions.[2] However, the same review also found "little high quality data for how best to prevent, diagnose and treat AWS in the ICU."[2] The first challenge is to identify patients at greatest risk for AWS. No validated tool exists for patients admitted to the ICU, but scoring tools for hospitalized patients in non-ICU settings (eg, the Prediction of Alcohol Withdrawal Severity Scale)[3] highlight the importance of previous withdrawal episodes, seizures, hallucinations, alcohol rehabilitation treatment, and other substance abuse. Various risk thresholds for the reported habitual quantity of alcohol consumed have been proposed, but no consensus has been reached.[2]

Several preventive strategies have been studied in critically ill patients considered at high risk of AWS, including ethanol, flunitrazepam, clonidine, clomethiazole, haloperidol, and diazepam, with disappointing or inconclusive results due to poor study design.[2] Most guidelines[4] for care in the ICU and elsewhere emphasize treatment over prophylaxis and require the development of specific symptoms and signs of alcohol withdrawal before medication administration. In the ICU context, this approach results in quicker symptom control, lower dose administered, and shorter sedative infusions compared with prophylactic administration,[5] along with shorter length of ICU stay.[6] Benzodiazepines, which act as $GABA_A$ agonists, are recommended as first-line medications for AWS,[4,7] although trial evidence for effectiveness among patients in the ICU is limited. Propofol, a $GABA_A$ agonist with additional sedative actions, is a useful adjunct in patients with benzodiazepine-refractory AWS.[8] Dexmedetomidine, an α-2 agonist, has been shown in 2 randomized trials to reduce benzodiazepine requirement compared with placebo in patients with AWS.[9,10]

Baclofen is a GABA type B ($GABA_B$) agonist labeled for use in the US and elsewhere as a treatment for reversible muscle spasticity. The usual oral dose of baclofen is 40 to 80 mg per day, and its most common adverse effect is sedation. However, following the self-published experience of a French physician who used higher doses of baclofen as a reportedly successful treatment for his own alcohol dependence,[11] baclofen has become an established, albeit unlicensed, treatment for this indication in France. The hypothesized mechanism involves inhibition of $GABA_B$-mediated alcohol-stimulated dopamine release in the amygdala[12] rather than an effect at $GABA_A$ receptors. In a 2013 survey of 296 French addiction specialists, 221 (74.6%) reported using baclofen for treatment of patients with alcohol use disorders.[11] In 2018, the French Agence Nationale de Sécurité du Médicament et des Produits de Santé recommended baclofen as a second-line treatment at doses up to 80 mg per day to help reduce alcohol consumption.[13] In 2018, based on select meta-analyses, a group of primarily European clinicians issued the "Cagliari Statement" that recommended baclofen as a second-line treatment aiming at abstinence in alcohol use disorder, but specifically stated that "baclofen should not be used instead of benzodiazepines in the treatment of [AWS], as there is no evidence of its efficacy in preventing the development of potentially life-threatening complications…such as seizures and delirium tremens."[14] A 2019 Cochrane review[15] identified only 4 randomized trials that compared baclofen with placebo, diazepam, and chlordiazepoxide as a treatment for AWS. Because the quality of these studies was "very low," the authors "could draw no conclusions about the efficacy and safety of baclofen for the management of AWS."[15]

These factors provide context for the randomized placebo-controlled clinical trial reported by Vourc'h et al[16] in this issue of *JAMA*. These French investigators studied the novel use of baclofen in patients who were receiving mechanical ventilation and were at risk of AWS, rather than those with

established manifestations. The threshold for inclusion was meeting the US National Institute on Alcohol Abuse and Alcoholism criteria for unhealthy alcohol use (ie, >14 units per week for men and 7 units per week for women or men older than 65 years; 1 unit corresponded to 1 drink that contains approximately 12 to 14 g of pure alcohol [eg, 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof liquor]). This alcohol intake level would not be considered an especially high or unhealthy level in many countries, including in France.[17] Patients were randomized to receive placebo (n = 155) or baclofen (n = 159), with doses adjusted from 50 to 150 mg per day based on estimated glomerular filtration rate, for up to 15 days. The baclofen dose was nearly twice of that currently recommended in France, although there are no ICU recommendations for use of baclofen for this indication. The investigators hypothesized that baclofen would reduce ICU-associated agitation given its known sedative effects and possible link to decreased alcohol craving. Unlike most AWS medication guidelines, baclofen was administered in this study without titration, rather than in response to known features of AWS risk or its early manifestations.

Characteristics of the 314 patients randomized in 18 hospitals were well-matched at baseline. The primary outcome was the percentage of patients with at least 1 prespecified agitation-related event. Agitation events occurred in significantly fewer patients who received baclofen than in those who received placebo (19.7% vs 29.7%; difference, −9.93% [95% CI, -19.45% to -0.42%]; P = .04). By day 28, a total of 71 patients (22.6%) died (39 [25.3%] in the baclofen group and 32 [21.6%] in the placebo group; P = .44). The competing risk of death for the primary outcome was addressed using 2 techniques: a cause-specific regression model and an analysis in which death was equated with an episode of agitation. These are appropriate techniques; in the first, the effect of baclofen for reducing agitation persisted, while in the second (which substantially biases toward the null result), the effect was not statistically significant.

Although baclofen was effective at reducing agitation in this population and did not have major adverse effects, the baclofen group had a longer median duration of mechanical ventilation (9.0 vs 8.0 days; difference, 2.0 days; P = .02) and longer length of stay in the ICU (14.0 vs 11.0 days; difference, 2.0 days; P = .01) compared with the placebo group.

Several important questions remain. Although 75% of recruited patients reportedly drank at least 4 drinks per day, many may have been at low risk of AWS. Selecting a patient population at a higher risk of AWS could increase the likelihood of observing a beneficial effect without including patients who experience primarily the adverse effects related to prolonged sedation. The post hoc analysis (eTable 4 in Supplement 2 of the report by Vourc'h et al[16]) provides some evidence that patients with the highest antecedent alcohol consumption had the greatest reduction in agitation with baclofen. A higher-risk population could also provide more certainty that treatment with baclofen, compared with standard care with benzodiazepines, does not increase the risk of alcohol withdrawal seizures. In addition, less prolonged sedation may occur with the use of a lower dose of baclofen or with the initiation and titration of baclofen only when signs of alcohol withdrawal appear. For now, these issues remain unanswered.

Reducing agitation in critically ill patients likely to experience AWS is important, but it is useful to examine the nature of the events that constituted "agitation" in this study (shown in eTable 5 in Supplement 2 of the article[16]). Removing medical devices (ie, pulling out lines, catheters, or drains) was the most common agitation-related event (46.6% of patients in the baclofen group vs 53.2% in the placebo group). Some of these agitation-related events might not have been associated with harm to the patient. Conversely, the 2 extra ICU days associated with baclofen are expensive and potentially detrimental.

Should this clinical trial by Vourc'h et al influence change practice? Results of the study suggest that high-dose baclofen reduced agitation-related events among individuals with a history of unhealthy alcohol use who require mechanical ventilation. However, because baclofen use was associated with longer time receiving mechanical ventilation and longer ICU stay, it may be more useful as a titrated adjunctive agent when more established treatments fail rather than as a first-line therapy. Until several important remaining questions are answered, the authors' following conclusion is sound: "further research is needed to determine the possible role of baclofen in this setting."

ARTICLE INFORMATION

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