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Propofol and the risk of delirium: Exploring the anticholinergic properties of propofol

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ABSTRACT

Delirium is a common pathologic event in both medical and surgical patients. It is essential to note that patients who develop delirium have worse long term outcomes. The etiology and pathogenesis of delirium are extremely complex and not entirely understood. Certain medications classes are implicated in delirium. For example, medications targeting muscarinic acetylcholine receptors are well known to be associated with delirium and altered mentation. Propofol is a medication commonly used in anesthesiology practice and sedation in intubated patients. In vitro studies provided evidence that propofol actively interacts with muscarinic acetylcholine receptors. Additionally, some, but not all clinical studies demonstrated that propofol led to delirium. Therefore, future prospective studies investigating the use of propofol and delirium occurrence are of paramount importance. These studies should adjust for such common confounders as patients' demographics and age, comorbid conditions, use of other medications, type of surgery, baseline cognitive status, etc. Another important task would be to research the susceptibility for propofol-related delirium. By studying these critical questions, we will gain additional insights into the complex etiology and pathobiology of delirium in addition to a better understanding of the pharmacology of propofol.

Introduction

Delirium is a common adverse outcome in patients after major surgery [1–6] as well as in medical patients [7]. Delirium is characterized by fluctuating disturbances in attention, memory, orientation, perception, psychomotor behavior and sleep [8–10]. The criteria for delirium, as described by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, are shown in Table 1.

Delirium tends to be diagnosed based on clinical suspicion and, therefore, may be under diagnosed [11]. Several clinically validated screening tools are available, which may help clinicians to detect delirium early [12–14]. It is relevant to note that delirium is independently associated with an increase in both short-term and long-term mortality [15].

The incidence of postoperative delirium varies by surgery type. For example, delirium after knee replacement occurs in 20–30% of patients. It is important to note that the incidence of postoperative delirium is higher after cardiac surgery, as demonstrated by several recent studies [16–18].

The etiology and pathogenesis of delirium is complex and not entirely understood. On a cellular level, alterations in neurohormonal signaling, inflammation, oxidative stress and apoptosis underlie the clinical manifestations of this disorder. From a clinical standpoint, several risk factors are well established and can be used to stratify the risk [19]. Some of these factors are presented in Table 2. However, recent research data suggest that some comorbid medical conditions such as obstructive sleep apnea may increase the risk of postoperative delirium [20–22].

It is well known that medications may contribute to the occurrence of delirium. The goal of this article is to review the current scientific literature on the propofol related increase in delirium risk. First, we will review the clinical reports on the impact of propofol on delirium. Second, possible mechanisms for propofol related delirium will be discussed. Third, the ways to investigate the risk of propofol related delirium will be discussed.

Hypothesis

Medications affecting cholinergic receptors are strongly associated with the development of delirium and confusion. Propofol, a medication which is commonly used in anesthesiology and critical care settings, may exert anticholinergic effects. Therefore, propofol

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Table 1
DSM-IV Criteria for Delirium.

(A) Disturbance of consciousness with reduced ability to focus, sustain, or shift attention
(B) A change in cognition (memory, language, or orientation) or the development of a perceptual disturbance not better accounted for by dementia
(C) Disturbance develops over a short period of time and tends to fluctuate during the course of the day
(D) There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition

Table 2
Common Risk Factors for Delirium.

Age >65 years
Male gender
Open cardiac surgery
Major medical comorbidity (infection, anemia, myocardial infarction etc.)
Alcohol withdrawal
Underlying neurological disease (stroke, tumor etc.) and cognitive dysfunction
Sleep deprivation
Iatrogenic (medications, urinary catheterization, dehydration etc.)
Metabolic and nutritional abnormalities
Pain
Fractures (particularly hip)
Depression and psychological stress

may provoke delirium in susceptible individuals and, therefore, greatly increase morbidity and mortality.

Propofol and delirium: clinical studies

Several reports in the literature implicate propofol in precipitating delirium. Gadalla and Spencer reported a case of prolonged delirium after administration of propofol [23]. Cohen et al. reported 2 cases: a healthy 55-year old woman who was given propofol for sedation during a colonoscopy and a 32 year old female who was given propofol for a dilation and evacuation procedure for a missed abortion [24]. Both of the cases had a complicated procedural course: in both patients central anticholinergic syndrome (a term synonymous with delirium) secondary to propofol injection was suspected, and the administration of physostigmine (acetylcholinesterase inhibitor, which increases the availability of acetylcholine) resulted in normalization of mental status. Palm et al. [25] described the case of a 20-year old female who became delirious after sedation with propofol; however, in this clinical case, the delirium was resolved by administering haloperidol. Snow et al. presented a case of a 20 year old male who presented for management of elbow dislocation [26]. The patient received propofol for anesthesia and shortly became combative and delirious. Further administration of propofol for sedation only resulted in worsening of agitation. Finally, physostigmine was administered which resulted in normalization of patient's agitation and delirious state.

Hasani et al. studied 83 children undergoing surgery to compare the rates of agitation between halothane and propofol [27]. These researchers demonstrated that propofol anesthesia was associated with approximately 3 times greater incidence of agitation compared to halothane. However, it is important to note that others reported that propofol was associated with less agitation compared to sevoflurane [28–31]. Patients' demographics and characteristics (including genetic predisposition) and type of surgery may explain these discrepant results.

What are the mechanisms of propofol related delirium: focus on anti-muscarinic properties of propofol

One mechanism through which propofol may precipitate delirium is by blocking muscarinic acetylcholine receptors (mAChRs) [32]. It is well established that drugs that block mAChRs, the so-called anticholinergic drugs, can precipitate delirium. Indeed, it is estimated that approximately 12–39% of all cases of delirium can be attributed to anticholinergic medications [33–35]. Anticholinergic activity can be found in many classes of drugs. Several commonly used drugs have moderate to high anticholinergic activity; these include tricyclic antidepressants, antihistamines like diphenhydramine, anti-Parkinson's drugs such as benztropine, and drugs affecting the gastric acid synthesis such as cimetidine and ranitidine [34]. Current therapies for overactive bladder, a chronic condition that affects over 17% of US adults, involve drugs that block mAChRs, including oxybutynin, tolterodine, trospium, darifenacin, solifenacin, and fesoterodine ER [36]; all of these agents are known to be associated with cognitive impairments, including delirium [36].

Although it is not generally appreciated, there are several studies reporting on propofol's ability to block muscarinic receptors. There are five subtypes of muscarinic receptors (M1 to M5) [37]. The first study focusing on propofol's interactions with mAChRs was conducted by Yamamoto et al. using an in vitro approach [38]. These researchers showed that the negative chronotropic effect (decrease in heart rate) of propofol on the ventricular myocytes was mediated via blocking of M2 receptors.

Nagase et al. examined the effects of propofol on mAChR-mediated signal transduction [39]. These investigators showed that propofol negatively affects the signal transduction at the level of the M1 receptor.

Murasaki et al. in an in vitro study showed that propofol inhibits the M1 receptor by disrupting the interaction between the receptor and associated signaling protein [40]. However, Hirota et al. failed to show that propofol significantly binds with M1, M2, or M3 receptors [41].

The effect of propofol on mAChRs has also been examined in humans. Xie et al. examined the effect of propofol-induced anesthesia on mAChR availability using positron emission tomography (PET) [42]. Six healthy volunteers were scanned during three stages: awake (before anesthesia), unconscious (under propofol-induced anesthesia), and recovery (after regaining consciousness post-anesthesia). The authors concluded that propofol induced unconsciousness is associated with reduced cholinergic activation in the central nervous system.

However, it is essential to emphasize that current data on the interrelationship between propofol administration and delirium is incomplete and controversial. Future studies of prospective methodology aiming to assess the impact of propofol on the incidence of delirium are needed. It will be essential for such studies to adjust for confounders such as patients' age, comorbidities, cognitive function at baseline, use of other medications commonly implicated to delirium etc. At the same time, it is likely that individual patient's susceptibility does play a key role in the occurrence of delirium irrespectively of the association with propofol. Future studies should also investigate the genetic markers for susceptibility of propofol related delirium.

Implications of the hypothesis

Delirium is a pathologic state with etiology and pathogenesis that are not well understood. However, it is well known that certain medication classes can provoke delirium in susceptible individuals. As was discussed above, propofol may interact with