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Effect of cannabis use on propofol requirement for ICU sedation

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Dear Editor,

Sedation and analgesia in critically ill patients are among the most important aspects of care delivery in the intensive care unit (ICU) [1]. It can be challenging when dealing with critically ill patients who have a history of substance abuse. Cannabis has analgesic, anxiolytic, antiemetic, and antispastic properties and has been in widespread use and abuse for thousands of years globally. Although some published case reports have shown that cannabis users demanded elevated doses of intravenous and inhaled anaesthetics during anaesthesia induction and/or maintenance [2, 3], data regarding cannabis and its interactions with commonly used sedative and analgesic agents in the ICU setting are scarce.

Flisberg *et al*. [4] in a prospective, randomized, single-blinded human study assessed the induction doses of propofol in patients using cannabis. This study included 30 male cannabis users and 30 control individuals. Induction doses of propofol to achieve the target bispectral index values were not significantly different in the 2 groups. However, in the cannabis user group significantly higher doses of propofol were required to achieve adequate sedation for successful laryngeal mask insertion. The authors concluded that to achieve satisfactory clinical response, higher doses of propofol are required in cannabis users. In addition, Imasogi *et al*. [5] implemented a case-control study on the correlation between cannabis use and propofol anaesthesia during endoscopy. In total 318 members participated (cases, $n = 151$; controls, $n = 167$) in this study. Their results indicated that cannabis exposure was concomitant with a rise in propofol dose. The authors concluded that cannabis consumption was significantly associated with the amount of propofol required for sedation in endoscopy.

An animal study Brand *et al*. [6] showed that Δ 9-Tetrahydrocannabinol (9-THC), the key psychoactive component of the cannabis plant, can significantly reduce the sedative effect of 50 mg kg^{-1} propofol in mice. Sedation could only be achieved by increasing propofol to toxic doses of 100 mg kg^{-1}. They concluded the existence of an antagonistic interaction between 9-THC and propofol.

We report a 38-year-old, 90 kg male with a history of a few pack-years tobacco smoking and cannabis consumption for over 10 years (with no clear description of its amount) admitted to the ICU postoperatively. There was no significant past medical or surgical history. In a motor vehicle accident, he sustained significant trauma to his anterior chest wall with no other injuries. His initial examination indicated an alert and oriented young man in respiratory distress. His heart rate was 110 min^{-1}, blood pressure 120/60 mmHg, respiratory rate 24 min^{-1}, and temperature 38.5°C. There were multiple injuries on the anterior chest wall and diminished breath sounds bilaterally. Abdominal, pelvic, extremities, and rectal examinations were within normal limits.

Emergency thoraco-abdominal surgery had to be undertaken to secure intrapleural bleeding, and abdominal exploration was performed for possible diaphragmatic or other occult injuries. The day after surgery

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he experienced shakiness, sweating, agitation, distress, restlessness, and remained on mechanical ventilation despite the multimodality pain and sedation management. Sedation/analgesia in the ICU was initiated with a propofol infusion of 50-300 mg h^{-1}, IV acetaminophen 1 g every 6 hours as needed (PRN), midazolam 1-5 mg every 3 hours PRN, morphine sulphates 5 mg every 3 hours PRN, and enteral clonidine 0.1 mg 3 times a day (TDS) on the first day then 0.2 mg TDS; on the second day he was haemodynamically stable. Although he received a total of 13,350 mg propofol, 56 mg midazolam, 45 mg morphine sulphate, 5 g acetaminophen, and 0.6 mg clonidine during the first 36 hours of his ICU stay, he remained anxious and agitated under mechanical ventilation, with a Ramsay sedation score of 1 [7]. We discontinued propofol and administered a fentanyl infusion of 100–300 µg h^{-1} with no other changes in ICU sedation/analgesia regimen, which resulted in a good response gradually within a few hours. He was extubated successfully 48 hours later after receiving a total of 2600 µg fentanyl, 15 mg morphine sulphate, 21 mg of midazolam, 0.6 mg clonidine, and 3 g acetaminophen.

The exact mechanism of interaction between propofol and cannabis remains unknown. Some animal models suggest that propofol may transmit some of its sedative effects through the endocannabinoid system. One hypothesis about the interaction of propofol and cannabis includes the reduction of the cannabinoid CB-1 receptor in chronic cannabis users versus partial agonism/antagonism of the CB-1 receptor by other phytocannabinoids in marijuana products that may compete with propofol [5, 6].

In addition, interactions at γ-aminobutyric acid type A ($GABA_A$) receptors were proposed for antagonism of propofol by Δ 9-tetrahydrocannabinol [6]. Consequently, it is possible that the addition of an *N*-methyl-*D*-aspartate (NMDA) receptor antagonist like ketamine, which does not have direct interaction with GABA receptor, could contribute to counteracting or attenuating the increased requirements of GABA-dependent anaesthetic agents such as propofol in active cannabis users [8]. Several mechanisms can explain the effect of NMDA receptor antagonists enhancing the effect of propofol. NMDA receptor blockade interrupts signalling and transduction through glutamatergic nerves enhancing the effects of propofol by increasing the input of dopamine in the nucleus accumbens playing a primary and dominant role, while glutamate signalling plays a secondary role in the process [9]. Nevertheless, the use of ketamine, depending on the dose, always implies the possibility of some adverse perioperative events like delayed emergence, mood changes, and other behavioural reactions in cannabis users. Ketamine (at least in anaesthetic doses) inhibits cytochrome p4503A4 (CYP3A4) enzyme expression, a key pathway of primary and secondary metabolization of the main psychoactive marijuana ingredients [10]. Ketamine infusion may be able to facilitate cannabis intoxication by decreasing the drug clearance rate from the body [11]. Therefore, NMDA-receptor antagonists do not seem to be an appropriate choice as an alternative for sedation of cannabis users in the ICU setting.

Other human studies indicated a synergy by co-administration of opioids with cannabis in managing peripheral inflammatory, acute, and chronic pain [12]. They postulated that cannabis and opioid receptors could interact at different levels, bringing about additive or synergistic properties for controlling anxiety and pain [12]. Furthermore, some studies showed a reciprocal relationship between the cannabinoid and opioid systems in dependency and the similarities between withdrawal symptoms including irritability, aggression, anxiety, sleep disturbance, and restlessness [13], which could be an explanation for the efficacy of opioids in cannabis withdrawal.

To the best of our knowledge, this is the first case report on cannabinoids' pharmacological interaction with propofol, used for sedation in the ICU setting. Based on the presented studies and our observations, we suggest that due to the potential antagonistic effects of cannabis on propofol, alternative agents such as opioids for ICU sedation should be considered in patients with a history of cannabis use. Future randomized studies are required to address this issue further.

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