CORRESPONDENCE

Ketamine-induced cholangiopathy in ARDS patients

Christian de Tymowski^{1,2,3,4}, François Dépret^{1,2,5,6*} , Emmanuel Dudoignon^{1,2,5}, Matthieu Legrand^{5,6,7} and Vincent Mallet^{1,2,8} on behalf of the Keta-Cov Research Group

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We read with interest the letter by Meersseman and colleagues [1]. The group reports four other cases of secondary sclerosing cholangitis (SCC) in critically ill coronavirus disease 2019 (COVID-19) patients, which suggests that critically ill COVID-19 patients could be at risk for SCC [2]. Risk factors of SCC in critically ill patients include biliary ischemia, high positive end-expiratory pressure, drug-induced bile duct injury and systemic inflammation [1]. There is mounting evidence that ketamine could contribute to SCC in critically ill, including COVID-19, patients. Ketamine has been widely used as a second-line sedative agent in intensive care units (ICUs) during the COVID-19 pandemic [2, 3]. In 2021, Bütikofer and colleagues compared 34 critically ill COVID-19 patients with 34 critically ill influenza patients [4]. Four patients in the COVID-19 group developed SCC compared to none in the influenza group despite a higher severity of influenza patients (i.e., higher sepsis related organ failure assessment (SOFA) score, higher simplified acute physiology (SAP) score II). All patients received ketamine in the COVID-19 group and none in the influenza group.

We have also observed an association between ketamine and SCC in a cohort of 293 patients with invasive mechanical ventilation after severe burn injury. From June 2012 (opening of our center) to April 2017 ketamine was largely prescribed (liberal period: 1–3 mg/

kg/h). In 2017, the French National Agency for the Safety of Medicine issued an alert on potential liver toxicities of ketamine. [5] Ketamine prescriptions were restricted (restrictive period: 0.01–0.05 mg/kg/h) thereafter. The liberal and the restrictive periods comprised 219 (75%) and 74 (25%) patients, respectively. Patient severity (i.e., age, total body surface area burned, abbreviated burned severity index, SAPS II score, initial prescription of nor-epinephrine) was identical (all p values > 0.2). Cholestasis at discharge was more frequent during the liberal compared to the restrictive period (33% vs 20% respectively, $p=0.04$). This difference was particularly striking for the more severe cholestasis (i.e., Alkaline phosphate ≥ 4 N) (Fig. 1). Finally, 9 (7.4%) SCC were diagnosed during the liberal period vs only 1 (1.4%) during the restricted period ($p=0.092$). We speculate that critically ill COVID-19 patients with SCC were overexposed to ketamine, leading to biliary precipitations of norketamine, biliary obstructions and cholangitis. Ketamine could act as a second hit in a previously injured biliary tract, either by SARS-CoV-2, (there is little, inconsistent, evidence that SARS-CoV-2 can infect biliary cells); by other medications; the systemic inflammatory response syndrome; and/or by ischemia. Providing the total cumulative dose of ketamine used during the ICU stay in the cases reported would be important to explore this potential contributing factor. Furthermore, a registry of critically ill patients with SCC including the dose of ketamine received seems necessary to better explore this potential severe side effect. Meanwhile, we do believe that ketamine-induced cholangiopathy should be suspected in COVID-19 patients with prolonged utilization or high doses of ketamine and increasing bilirubin.

*Correspondence: francois.depret@aphp.fr

¹ Department of Anesthesiology and Critical Care and Burn Unit, Assistance Publique—Hôpitaux de Paris (AP-HP), Groupe Hospitalier St-Louis-Lariboisière, Paris, France
Full author information is available at the end of the article

The members of the Keta-Cov Research group are listed in the Acknowledgement section.

Abbreviations

COVID-19: coronavirus disease 2019; SCC: secondary sclerosing cholangitis; SAPSI: simplified acute physiology score II.

Author details

¹ Department of Anesthesiology and Critical Care and Burn Unit, Assistance Publique—Hôpitaux de Paris (AP-HP), Groupe Hospitalier St-Louis-Lariboisière, Paris, France. ² University de Paris, Paris, France. ³ Centre de Recherche sur l'Inflammation (CRI), INSERM U1149, Paris, France. ⁴ Laboratoire d'Excellence (Labex) Inflammex, ComUE Sorbonne Paris Cité, Paris, France. ⁵ Institut National de La Santé Et de La Recherche Médicale (INSERM), UMR INSERM 942, Lariboisière Hospital University Paris Diderot, 75475 Paris, France. ⁶ F-CRIN INI-CRCT Network, Nancy, France. ⁷ Department of Critical Care and Peri Operative Medicine, University of California, San Francisco, USA. ⁸ AP-HP Centre, Groupe Hospitalier Cochin Port Royal, DMU Cancérologie Et Spécialités Médico-Chirurgicales, Service d'Hépatologie, Université de Paris, Paris, France.

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sur l'inflammation, Inserm, UMR 1149. Paris, France; Amandine Landrieux,⁸ Pierre-Emmanuel Rautou, Université de Paris, AP-HP, Hôpital Beaujon, Service d'Hépatologie, DMU DIGEST, Centre de Référence des Maladies Vasculaires du Foie, FILFOIE, ERN RARE-LIVER, Centre de recherche sur l'inflammation, Inserm, UMR 1149. Paris, France; Laurent Chouchana, Université de Paris, AP-HP, Hôpital Cochin, DMU PRIME, Service de pharmacovigilance, Paris, France; Coralie Gernez, 3. Université de Paris, AP-HP, Hôpital Louis Mourier, DMU ESPRIT, Service de Réanimation Médico-Chirurgicale, Colombes, France; Carole Burger, Université de Paris, AP-HP, Hôpital Necker Enfants Malades, DMU CARTE, Service de Néphrologie et de Transplantation rénale, Paris, France; Anne Scemla, Université de Paris, AP-HP, Hôpital Necker Enfants Malades, DMU CARTE, Service de Néphrologie et de Transplantation rénale, Paris, France; Lionel Lamhaut, Université de Paris, AP-HP, Hôpital Necker Enfants Malades, Département d'Anesthésie Réanimation, Paris, France; Rémi Flicoteau, Université de Paris, AP-HP, Hôpital Saint Louis, DMU PRISME, Service de Biostatistique et information médicale, Paris, France; Jean-Paul Duong Van Huyen, Centre Hospitalier René Dubos, Service de Réanimation Médico-chirurgicale, 95,300 Pontoise, France; Jean-Michel Correas, Université de Paris, AP-HP, Hôpital Necker Enfants Malades, Département d'Anesthésie Réanimation, Paris, France; Heiner Wedemeyer, Stanislas Pol, Université de Paris, AP-HP, Hôpital Cochin, DMU Cancérologie et spécialités médico-chirurgicales, Service d'Hépatologie, Paris, France.

Author contributions

FD: conception of the study, acquisition, analysis and interpretation of the data, draft of the manuscript; CT, FD, ED, ML, VM: conception of the study, acquisition, analysis and interpretation of the data, edition of the manuscript. The authors declare they have seen and approved the final version of the manuscript. All members of the Keta-Cov group facilitated the study or took care of the reported patients.

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