Intensive Care Medicine

Intravenous ketamine and progressive sclerosing cholangitis in Covid-19 patients

--Manuscript Draft--

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Author Comments:	Dr. Giuseppe Citerio Editor in chief Intensive care medicine Paris, February 11, 2021 Dear Dr. Citerio, As a reply to Dr. Chanques et al. recommendations on analgesia and sedation in patients with ARDS, (1) please find a letter entitled “Intravenous ketamine and progressive sclerosing cholangitis in Covid-19 patients” for evaluation as a piece to the correspondence series in Intensive Care Medicine. Our purpose, with this letter, is to inform the readership of Intensive Care Medicine that ketamine, a second-line drug recommended by Dr. Chanques et al. for sedation of ARDS patients, including those with Covid-19, can be associated with severe, potentially lethal, liver injury. Ketamine liver toxicities were first reported in 2009 in street users. Ketamine sclerosing cholangitis was reported in 2015, (2) 2017, (3) and 2019 (4, 5) in ICU patients, including patients with polytrauma, cardiac surgery, and severe burn injury. In our letter, we describe the liver outcomes of five Covid-19 patients with progressive cholangiopathy after exposure to intravenous ketamine during the first European pandemic wave.(The keta-Cov research group, J Hepatol, in press) All patients received ketamine doses within the thresholds recommended by Dr. Chanques et al. Liver injury was consistent with all reports on ketamine liver toxicities in street users, in burned patients, and with one Covid-19 patient from the USA. (6) Liver injury was also consistent with several patients with ‘unexplained’ post-Covid sclerosing cholangitis. (7-9) Our message is that ketamine could contribute to liver injury (and maybe AKI) of Covid-19 patients undergoing mechanical ventilation and should not be given for maintenance sedation, or with close monitoring of liver tests. We think that Dr. Chanques et al. should post an addendum to their article to inform readers on the risks associated with ketamine analgesia and sedation. We hope that the editorial board will find our manuscript suitable for evaluation and publication. Most sincerely, Pr. Vincent Mallet, Université de Paris; AP—HP, Paris, France Phone: + 33 6 14 08 20 96

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Suggested Reviewers:	Dominique Larrey dom-larrey@chu-montpellier.fr Pr. Larrey is an expert in the field of drug induced liver injury, has reported on ketamine liver toxicity

Commentary

Intravenous ketamine and progressive sclerosing cholangitis in Covid-19 patients

The keta-Cov research group*

Running title: Ketamine and progressive cholangiopathy

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Footnote page

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List of abbreviations

ARDS: acute respiratory distress syndrome; Covid-19: Coronavirus infectious disease 2019

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Authors' contributions: VM: conception of the study, acquisition, analysis and interpretation of the data, draft of the manuscript; ND, JDR, KB, SP: 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.

Commentary

In the November 10, 2020 issue of Intensive Care Medicine, Chanques et *al.* recommended lower dose (0.1–1 mg/kg/h) and higher dose (1-3 mg/kg/h) of ketamine as a second-line agent for analgesia and maintenance sedation of acute respiratory distress syndrome (ARDS) patients undergoing mechanical ventilation, respectively.(1) Ketamine is off-label in this indication (Europe, USA, and Canada), and we think that Dr. Chanques et *al.* did not take into account, before establishing their recommendations, the safety issues, including liver toxicities, associated with high cumulative doses of ketamine. Ketamine liver injury, including sclerosing cholangitis, was first reported in 2009, in street users from Hong-Kong (China).(2) Critical care sclerosing cholangitis was associated with ketamine in 2015 in a series of ICU patients from Berlin (Germany).(3) In 2017, the French National Drug Agency issued an alert after the report of 10 cases of liver disease, including end-stage liver disease, in burned patients exposed to ketamine for a long period and/or at higher doses. In 2020, we have observed five Covid-19 patients from five distinct tertiary centers (one in Germany, and four in France) with sclerosing cholangitis after exposure to intravenous ketamine during the first European pandemic wave. (The keta-Cov research group, J Hepatol, in press) Liver injury was dose-dependent, progressive, and total cumulative ketamine dose correlated with outcome, including two liver-related deaths and one, overt, sclerosing cholangitis. The two patients with liver death had received, according to Dr. Chanques, higher dose of ketamine (2.2 mg/kg/h) for 16 and 14 days, respectively. The patient with sclerosing cholangitis had received, according to Dr. Chanques, lower dose of ketamine (0.16 mg/kg/h), but for 26 days, which corresponded to the longest period in the series. The other two patients had infraclinical chronic cholestasis at the last follow up visit, eight months after ketamine cessation. All patients had a normal liver before Covid-19. There was no other risk factor for critical

care cholangiopathy: none had profound hypoxemia and none had severe shock. All patients had developed jaundice under ketamine and the level of total serum bilirubin in the ICU was closely related to total cumulative ketamine dose ($R^2 = 0.95$). Liver injury was not associated with Covid-19 severity. All patients progressed to acute kidney injury (AKI) under ketamine, and three required renal replacement therapy. Endoscopic retrograde cholangiopancreatography showed biliary obstructions with biliary casts and rarefaction of the intrahepatic biliary tracts. Ketamine undergoes extensive metabolism in the liver, initially via nitrogen demethylation to norketamine: a 100% water-insoluble by-product. Forensic studies have shown that norketamine is present in human bile (and in the urine) after ketamine poisoning.(4) We speculate that over-exposition to ketamine may lead to biliary precipitation of norketamine, biliary obstructions, cholangitis, and secondary biliary cirrhosis. Whether ketamine contributed to AKI is beyond the scope of this small, observational study, but deserves attention. We think that clinicians should refrain from using ketamine to sedate ARDS patients, including those with Covid-19. If cornered to such a prescription, a short-term period and a close monitoring of bilirubin is mandatory. We have issued an alert.

499/500 words

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