Journal of
Clinical Medicine

MDPI

Comment

Avoiding, Not Managing, Drug Withdrawal Syndrome in the Setting of COVID-19 Acute Respiratory Distress Syndrome. Comment on Ego et al. How to Manage Withdrawal of Sedation and Analgesia in Mechanically Ventilated COVID-19 Patients? *J. Clin. Med.* 2021, *10*, 4917

Fabrice Petitjeans [1], Marc de Kock [2], Marco Ghignone [3] and Luc Quintin [1,*]

[1] Critical Care, Hôpital d'Instruction des Armées Desgenettes, 69008 Lyon, France; fabricepetitjeans@yahoo.fr
[2] Critical Care, Centre Hospitalier de Wallonie Picarde, 7500 Tournai, Belgium; marcdekock1888@gmail.com
[3] Critical Care, JF Kennedy North Hospital, West Palm Beach, FL 33407, USA; torchio@aol.com
* Correspondence: lucquintinx@gmail.com

Citation: Petitjeans, F.; de Kock, M.; Ghignone, M.; Quintin, L. Avoiding, Not Managing, Drug Withdrawal Syndrome in the Setting of COVID-19 Acute Respiratory Distress Syndrome. Comment on Ego et al. How to Manage Withdrawal of Sedation and Analgesia in Mechanically Ventilated COVID-19 Patients? *J. Clin. Med.* 2021, *10*, 4917. *J. Clin. Med.* **2022**, *11*, 3336. https://doi.org/10.3390/jcm11123336

Academic Editor: Sukhwinder Singh Sohal

Received: 14 January 2022
Accepted: 8 June 2022
Published: 10 June 2022

The management of sedation in the setting of COVID-19 ("COVID") by Ego et al. [1] does not combine pathophysiology and pharmacology. Their premise rests on «*decreasing the work of breathing, applying lung protective ventilation and limiting asynchronies [to] minimize the risk of ventilator-induced lung injury (VILI) . . . . . COVID-19 patients require high [doses] of sedatives, analgesics and neuromuscular blocking agents (NMBA) . . . . . frequently for more than 7 days*» [1]. Ego manages the drug withdrawal syndrome but does not *avoid* it.

First, the requirements allowing for optimal ventilation in the setting of acute respiratory distress syndrome (ARDS), delineated earlier [2–4], are not addressed: *(Vt, f) = f(temperature, agitation, inflammation, lung water, pH, microcirculation, $PaCO_2$, PaO_2, positioning)*. Briefly, temperature is lowered to low normal (35–36 °C). Alpha-2 agonists suppress the tonic activity of the dorsal noradrenergic bundle [5], control agitation and avoid emergence delirium and withdrawal syndrome [6] («cooperative » sedation from endotracheal intubation onward, i.e., alpha-2 agonist as *first*-line sedative [7]: clonidine 2 μg kg^{-1} h^{-1} or dexmedetomidine 1.5 μg kg^{-1} h^{-1}). To achieve $-2 < RASS < 0$ (stringent restlessness), alpha-2 agonists are supplemented with neuroleptics, if required (appendix in [8]), as in refractory delirium tremens [9]. Both drugs do *not* depress respiratory genesis [10]. Thus, conventional sedation is *not* needed following intubation. Adequate iterative circulatory optimization combined to the sympatholysis evoked by alpha-2 agonists normalizes the microcirculation, systemic pH, lactate concentration, CO_2 gap and venous O_2 saturation. Alpha-2 agonists present anti-inflammatory properties [11], either at the systemic or central nervous system or lung (tissue or receptors) level. In turn, normalized microcirculation eases diapedesis and improves the innate immune function: a return to normal functioning of the adrenergic receptors of immune cells possibly occurs ("upregulation").

Second, alpha-2 agonists act via the sympathetic and the parasympathetic systems, beginning with intubation: cooperative sedation [12], with improved cognition [13,14], diuresis, lowered VO_2 and inflammation, etc. As alpha-2 agonists evoke indifference to the environment and pain, opioids are counterproductive. Should the patient need analgesia, opioid free analgesia (appendix in [8]) does not depress respiratory genesis. Consequently, the duration of paralysis is reduced to a few hours in the setting of conventional ARDS (e.g., aspiration, etc.). Once the vicious circle of self-induced lung injury (SILI) is broken, spontaneous breathing resumes (e.g., pressure support delineated in [2–4]). PEEP is adjusted to a high level if diffuse ARDS is present. Upright position is set, meticulously.

Early COVID-ARDS presents with a high VA/Q ratio (lowered perfusion with near-normal ventilation, compliance, and lung mechanics). The inflammation of the lung capillaries and receptors and alveoli is addressed non-specifically. As COVID-19 does

not weaken the ventilatory muscles, and as compliance is relatively high, brief paralysis *just* breaks the SILI and the high inspiratory drive. Spontaneous breathing avoids ventilator-induced lung injury. First-line, high-dose alpha-2 agonists combined to low normal temperature and normalized inflammation do not lead to «*high regimen and prolonged use of sedative, analgesics and neuromuscular agents*» [1]. In our hands [3], breaking up the SILI is achieved within 2 days with a low toll (mortality: 8.5% [3]), at variance with general anesthesia, paralysis and proning for weeks with critical care clogging and societal consequences. This [3,4] requires demonstration.

Author Contributions: Conceptualization: F.P., M.d.K., M.G. and L.Q.; writing—original draft preparation, F.P., M.d.K., M.G. and L.Q.; writing—review and editing, F.P., M.d.K., M.G. and L.Q. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: L. Quintin received honoraria and unrestricted research grants from Boehringer-Ingelheim, France; UCB Pharma, Belgium; and Abbott International, Chicago, Il (1986-96), and holds US patent 8 703 697: method for treating early severe diffuse acute respiratory distress syndrome. The off-label use of dexmedetomidine and clonidine is disclosed. The other authors report no conflict of interest.

References

1. Ego, A.; Halenarova, K.; Creteur, J.; Taccone, F.S. How to Manage Withdrawal of Sedation and Analgesia in Mechanically Ventilated COVID-19 Patients? *J. Clin. Med.* **2021**, *10*, 4917. [CrossRef] [PubMed]
2. Petitjeans, F.; Pichot, C.; Ghignone, M.; Quintin, L. Early severe acute respiratory distress syndrome: What's going on? Part II: Controlled vs. spontaneous ventilation? *Anaesthesiol. Intensive* **2016**, *48*, 339–351. [CrossRef] [PubMed]
3. Petitjeans, F.; Martinez, J.; Danguy des Deserts, M.; Leroy, S.; Quintin, L.; Escarment, J. A centrally acting antihypertensive, clonidine, sedates patients presenting with acute res-piratory distress syndrome evoked by SARS-coronavirus 2. *Crit. Care Med.* **2020**, *48*, e991–e993. [CrossRef] [PubMed]
4. Petitjeans, F.; Leroy, S.; Pichot, C.; Ghignone, M.; Quintin, L.; Constantin, J.M. Does Interrupting Self-Induced Lung Injury and Respiratory Drive Expedite Early Spontaneous Breathing in the Setting of Early Severe Diffuse Acute Respiratory Distress Syndrome? *Crit. Care Med.* **2021**. *Online ahead of print*. [CrossRef] [PubMed]
5. Saunier, C.F.; Akaoka, H.; de La Chapelle, B.; Charlety, P.J.; Chergui, K.; Chouvet, G.; Buda, M.; Quintin, L. Activation of brain noradrenergic neurons during recovery from halothane anesthesia: Persistence of phasic activation after clonidine. *Anesthesiology* **1993**, *79*, 1072–1082. [CrossRef] [PubMed]
6. Gold, M.S.; Redmond, D.E.; Kleber, H.D. Clonidine blocks acute opiate-withdrawal symptoms. *Lancet* **1978**, *2*, 599–602. [CrossRef]
7. Pichot, C.; Ghignone, M.; Quintin, L. Dexmedetomidine and clonidine: From second- to first-line sedative agents in the critical care setting? *J. Intensive Care Med.* **2012**, *27*, 219–237. [CrossRef] [PubMed]
8. Pichot, C.; Longrois, D.; Ghignone, M.; Quintin, L. Dexmédetomidine et clonidine: Revue de leurs propriétés pharmacodynamiques en vue de définir la place des agonistes alpha-2 adrénergiques dans la sédation en réanimation. *Ann. Françaises D'anesthésie Réanimation* **2012**, *31*, 876–896. [CrossRef]
9. Carrasco, G.; Baeza, N.; Cabre, L.; Portillo, E.; Gimeno, G.; Manzanedo, D.; Calizaya, M. Dexmedetomidine for the Treatment of Hyperactive Delirium Refractory to Haloperidol in Nonintubated ICU Patients: A Nonrandomized Controlled Trial. *Crit. Care Med.* **2016**, *44*, 1295–1306. [CrossRef] [PubMed]
10. Voituron, N.; Hilaire, G.; Quintin, L. Dexmedetomidine and clonidine induce long-lasting activation of the respiratory rhythm generator of neonatal mice: Possible implication for critical care. *Respir. Physiol. Neurobiol.* **2012**, *180*, 132–140. [CrossRef]
11. Petitjeans, F.; Geloen, A.; Pichot, C.; Leroy, S.; Ghignone, M.; Quintin, L. Is the Sympathetic System Detrimental in the Setting of Septic Shock, with Antihypertensive Agents as a Counterintuitive Approach? A Clinical Proposition. *J. Clin. Med.* **2021**, *10*, 4569. [CrossRef] [PubMed]
12. Dollery, C.T.; Davies, D.S.; Draffan, G.H.; Dargie, H.J.; Dean, C.R.; Reid, J.L.; Clare, R.A.; Murray, S. Clinical pharmacology and pharmacokinetics of clonidine. *Clin. Pharm.* **1976**, *19*, 11–17. [CrossRef] [PubMed]
13. Mirski, M.A.; Lewin, J.J., 3rd; Ledroux, S.; Thompson, C.; Murakami, P.; Zink, E.K.; Griswold, M. Cognitive improvement during continuous sedation in critically ill, awake and responsive patients: The Acute Neurological ICU Sedation Trial (ANIST). *Intensive Care Med.* **2010**, *36*, 1505–1513. [CrossRef] [PubMed]
14. Arnsten, A.F.; Jin, L.E. Guanfacine for the treatment of cognitive disorders: A century of discoveries at Yale. *Yale J. Biol. Med.* **2012**, *85*, 45–58. [PubMed]