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Propofol infusion syndrome in severe COVID-19

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Editor—A recent Correspondence by Lönnqvist and colleagues[1] regarding a possible link between prolonged propofol infusion and increased risk of critical illness myopathy in the coronavirus disease 2019 (COVID-19) population inspired us to report a case of suspected propofol infusion syndrome (PIS) from late April 2020, during the spike of the COVID-19 pandemic. An otherwise healthy 55-yr-old man was transferred to our ICU from another centre after 9 days from the first symptoms of severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2), who had presented with fever up to 38.5°C, headache, and progressive shortness of breath (reported with patient consent). A thoracic CT scan showed a diffuse ground-glass pattern, more evident on the left lower lobe. He had been treated with a course of azithromycin and hydroxychloroquine, discontinued because of intolerance, followed by ceftriaxone. On the day of referral, both clinical and radiological signs of further pulmonary involvement prompted transfer to a specialised centre, where the APACHE II score on admission was <10. A short trial of noninvasive ventilation with FiO_2 of 0.5 did not produce clinical improvement, so mechanical ventilation was started after nasotracheal intubation.

Sedation was optimised using propofol 2% infusion as the sole hypnotic drug, with cardiovascular support from continuous infusions of norepinephrine and dobutamine, which ensured both good compliance for mechanical ventilation and satisfactory MAP. On day 2, clonic seizures were noticed on the patient's face, with progressive involvement of the right upper arm, which improved with boluses of midazolam i.v. CT showed no acute cerebral lesions, a CSF examination gave no meaningful results and SARS-CoV-2 RT–PCR testing of CSF was negative.

Multiple EEG recordings showed a general slowing with theta-delta dominance, disrupted by generalised slow-wave activity, that, together with the clinical persistence of clonus, led to inducing burst suppression through high-dose propofol infusion. The coexisting pulmonary compromise required deepening of sedation in order to resolve initial patient–ventilator desynchronisation, reaching on day 3 an infusion dose of propofol of 7.5 mg kg^{-1} h^{-1} and 0.2 mg kg^{-1} h^{-1} for midazolam based on actual body weight (70 kg). On the same day, progressive lactic acidosis developed, with a nadir of measured pH of 7.31 and a maximum serum lactate concentration of 5.1 mM. Worsening cardiovascular instability required higher doses of vasopressors, and acute kidney failure ensued. Continuous ECG monitoring showed alterations confirmed by ECG analysis (Supplementary material) with diffuse negative T waves and a QTc lengthening beyond 500 ms. Severe hypophosphataemia was interpreted as a herald of rhabdomyolysis. These data led to the suspicion of PIS, which prompted the immediate suspension of propofol infusion and the beginning of continuous renal replacement therapy.

Table 1 Timeline of pharmacological and laboratory data.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 12	Day 22
Propofol average dose (mg kg^{-1} h^{-1})	4.57	7.17	7.49	Stop propofol infusion				
Cumulative propofol dose (mg kg^{-1})	109.6	282	431	–				
Norepinephrine dose (μg kg^{-1} min^{-1})	0.17	0.19	0.33	0.33	0.24	0.14	0.04	–
C-reactive protein (mg L^{-1})	240	320	300	301.7	160	57	32	9.4
Procalcitonin (μg L^{-1})	3.5	3.4	2.5	3.5	2.9	1.5	0.9	0.3
Creatinine (mM)	80	107	139	158	163	218	118	321
Blood urea nitrogen (mM)	6.0	4.6	5.2	5.99	5.6	13.8	6.9	17.2
Aspartate aminotransferase (U L^{-1})	33	59	22	185	239	188	206	47
Alanine aminotransferase (U L^{-1})	66	69	68	1838	1253	857	274	57
Creatine phosphokinase (U L^{-1})	N.A.	N.A.	N.A.	N.A.	33 221	18 069	1907	136
Myoglobin (μg L^{-1})	N.A.	N.A.	N.A.	N.A.	14 148	7126	2592	299
Phosphate (mM)	0.51	0.58	0.12	1.54	1.37	1.1	1.09	1.95
Lactate (mM)	1.4	1.5	5.1	2.7	1.8	0.9	0.7	0.9
Base deficit (mM)	0.2	1.7	−0.6	−4.6	−1.2	−2.1	−0.6	2.8
High sensitivity troponin I (ng L^{-1})	36	N.A.	6.2	55	20	6	6	2.5
Plasma triglycerides (mM)	4.38	8.15	16.41	–	–	6.76	5.3	4.1
Albumin (g L^{-1})	23	22	18	N.A.	20	22	24	29

During the following days, ECG alterations, arterial pH, and serum lactate concentrations rapidly corrected. Serum CPK concentrations peaked at 33 000 U L^{-1} and myoglobin at 14 000 μg L^{-1}, while aspartate and alanine aminotransferases reached 1059 and 197 U L^{-1}, respectively. A timeline of pharmacological and laboratory data is shown in Table 1. The neurological status was monitored through a second cerebral scan and multiple EEG samplings. A slow tapering of sedation revealed no major neurological sequelae, cardiovascular support was suspended on the seventh day, and the patient was extubated on the 12th day; continuous renal replacement therapy was continued until the 15th day since arrival.

Discharge to a sub-ICU was organised after 22 days from referral. The main risk factors[2] for PIS in this case were the high-dose propofol infusion maintained for longer than 24 h and the need for vasopressor and inotropic therapy; the admission APACHE II score was low, however, and the patient was not receiving corticosteroid treatment. As stressed by the recent review by Hemphill and colleagues,[2] the foremost therapeutic decision was the immediate change of sedation strategy from propofol to a combination of midazolam and dexmedetomidine; coexistence of acute kidney injury with rhabdomyolysis and severe alteration of serum ion concentrations induced us to initiate continuous renal replacement therapy, which helped with both clearing the residual propofol concentration and restoring electrolyte homeostasis. Some authors[3,4] suggest a dextrose infusion as part of PIS therapy, which was already part of our patient's parenteral nutrition strategy.

There are currently limited data on neurological involvement in COVID-19, and we cannot link with certainty the epileptic manifestations in our patient with the viral syndrome.[5,6] Such manifestations, which normally lead us to deepen the level of sedation, can coexist with an acute respiratory distress syndrome that again often demands deep sedation and relaxation in order to optimise ventilation and reduce the risk of ventilator-induced lung injuries. In the context of COVID-19, the possibility of PIS should be considered, reinforcing the suggestion of Lönnqvist and colleagues[1] to rethink our sedation strategies in COVID-19 patients.

Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.08.020.

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