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Letters

ST-Segment Elevation, Brugada Syndrome, and Propofol?

Is This the Only Thing We Should Be Noticing?

We read with great interest the paper by Bergonti et al.[1] It clearly demonstrates the complexity of the electrocardiographic-based differential diagnosis process whenever multiple electrocardiogram (ECG)-interfering factors are simultaneously present.

We mostly agree with the analysis of the case report and the concomitantly provided differential diagnosis. Nevertheless, as the authors themselves expressed, we are not unequivocally certain that a propofol infusion syndrome (PRIS) is the culprit for the presented ECG pattern. From the information provided, a 4 mg/kg/h[1] infusion was administered, which according to current guidelines is considered a safe infusion regimen and is advocated as a maximal dose to avoid PRIS.[2]

During their differential diagnosis exercise, the authors listed several other conditions deemed capable of inducing related ECG pattern changes: intracranial hypertension, hypothermia, and Brugada syndrome. From the information provided, we believe it is unlikely that this could be a case of PRIS, because both a normal pH level and renal function were described along with an acceptable propofol infusion dosing regimen and the absence of hyperlactatemia. In this line of thought, it should be noted that the reader was only given one static maintenance dose of propofol. Considering the idiosyncratic and variable intrapatient pharmacodynamics of propofol, we believe that, although certainly not impossible, it is highly unlikely that this dose was rigidly applied from the beginning to the end of his induced coma.[3] Often, such doses are adjusted to the patient's hemodynamics and Richmond Agitation Scale Score and/or electroencephalographic parameters. Moreover, we would like to remind the readers that the risk of propofol-induced malignant ventricular arrhythmias even in patients with Brugada syndrome has not been demonstrated. On the contrary, recent research could not provide evidence of the alleged arrhythmogenicity of propofol in such patients.[4,5] Currently, a prospective study for investigating those effects is ongoing (EudraCT Register: 2019-004750-28)

Regarding the normalization of the ECG 40 hours after the withdrawal from a 7-day propofol infusion, it can be speculated that the phenomenon might be related to propofol. Nevertheless, propofol has a relatively short context-sensitive half-time, with plasma concentrations decreasing by 50% within a few hours, so it can likewise be speculated that the plasmatic/effect-site concentrations would have normalized significantly before the 40-hour time mark. Additionally, we assume from the case presentation that by stopping the propofol infusion, other clinical conditions were optimal to allow the patient to awaken (ie, a normal intracranial pressure and core temperature). Therefore, the discontinuation of propofol is intrinsically intertwined with the normalization of other potential culprits of ECG changes.

Such multifactorial considerations corroborate the authors' view on the difficulty of pinpointing a pathophysiological mechanism for the observed ECG changes. For assessing causality in complex situations, structured methods such as the World Health Organization-Uppsala Monitoring Centre system for standardized case causality assessment have been proposed, as well as more complex methods such as the method by Kramer et al.[6,7] According to these methods, the responsibility of propofol would be considered "unlikely" due to the lack of a dose-dependent relationship, the timing, and the presence of brain injury.

Altogether, we would like to emphasize that vigilance for conditions that have been demonstrated or are currently under investigation for provoking similar ECG changes is crucial to avoid the occurrence of malignant arrhythmic events.

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REPLY: ST-Segment Elevation, Brugada Syndrome, and Propofol? Is This the Only Thing We Should Be Noticing?

We read with interest the letter by Dr Flamée and colleagues and we would like to compliment them for their extensive analysis. Specifically, they question our diagnosis of propofol infusion syndrome (PRIS) mainly based on 3 observations: the absence of a causative connection; the absence of systemic manifestations; and the lack of a dose/time-dependent relationship. We find all these observations well-presented and certainly appropriate. Nevertheless, we still believe that PRIS is the most likely diagnosis in this patient.

Dr Flamée and colleagues assume that "by stopping propofol, other clinical conditions were optimal to allow the patient to awaken." Actually, propofol was discontinued due to the suspicion of PRIS.[1] Deep sedation was maintained with midazolam. After propofol was withdrawn, an increase in intracranial pressure was observed. However, despite persistently high intracranial pressure, the ST-segment elevation normalized. Dr Flamée and colleagues doubt the temporal relationship between propofol withdrawal and electrocardiogram (ECG) normalization due to the short half-life of this drug. However, Vernooy et al[2] previously demonstrated that PRIS is not the result of the direct effect of high-dose propofol. They suggested that propofol may have an indirect effect, shifting the balance of current in the outward direction and facilitating the development of ST-segment elevation, which slowly normalizes, later than propofol clearance from the blood. Indeed, the resolution of the ECG abnormalities up to 48 hours after propofol discontinuation has already been described.[3] The third doubt raised by Dr Flamée and colleagues is the absence of PRIS-related systemic manifestations. However, 2 case series already showed that ECG abnormalities may develop in the absence of systemic manifestation, in up to 28% of the patients.[2,4] Finally, we agree with Dr Flamée and colleagues stating that the risk of propofol-induced malignant ventricular arrhythmias has not been completely demonstrated in patients with Brugada syndrome. However, PRIS is a different entity that can affect patients with and without Brugada syndrome.[2,3] Re-evaluating the case with the "World Health Organization-Uppsala Monitoring Centre system for standardized case-causality assessment," as suggested by Dr Flamée and colleagues, we can conclude that PRIS is the probable/likely diagnosis, supported by reasonable time relationship, response to withdrawal, and ECG abnormalities unlikely to be (entirely) attributed to other disease or drugs.

To conclude, more than the final diagnosis, our case aims to highlight the complexity of the ECG differential diagnosis, whenever multiple interfering factors are simultaneously present. Patients with PRIS are often severely ill, and the concomitant use of vasopressors, inotropes, and high-dose sedation make the comprehension of this condition elusive.

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