Correspondence

Dexmedetomidine, agitated delirium, and "off-label" drugs

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We appreciate the comments by Parker *et al.* (1) and Knauert *et al.* (2) concerning our recent manuscript entitled "Dexmedetomidine for the treatment of hyperactive delirium refractory to haloperidol in non-intubated ICU patients: A non-randomized controlled trial" (3). We are agreed with the most of reviewer's considerations. However, we would like to add three reflections that may be interesting for the readers. The first relates to the current position of this alpha-2 agonist on the healthcare market. A second comment intends to respond to some interesting assertions from the reviewers that, in our opinion, could be controversial. The third and final comment is addressed to reflect on the future of the research on intensive care unit (ICU) delirium.

The first comment refers to the restricted indications of dexmedetomidine in ICUs setting. This drug was approved in the United States by the Food and Drug Administration (FDA) in late 1999 for use in humans as sedation of initially intubated and mechanically ventilated patients during treatment in an ICU setting, and sedation of non-intubated patients prior to and/or during surgical and other procedures. Subsequently this agent was approved also by the European Medicines Agency (EMA) for the same restricted indications. Consequently, dexmedetomidine has been especially studied for sedation in intubated patients. It has been widely compared with standard ICU intravenous sedation (propofol, midazolam lorazepam...) (4,5). Although dexmedetomidine provided some minor advantages (such as longer adequate sedation level) compared with standard ICU sedatives, the available evidence has shown that its main advantage is the control of delirium symptoms in intubated patients (an indication that was not included by authorizing its use).

Although agitated delirium in intubated patients is a major problem, in the non-intubated this problem can be even greater. This is due to two reasons. The first is the different prevalence of delirium in these populations. In our environment, agitated delirium does not exceed 8% in intubated patients whilst it is greater than 25% in non-intubated patients (6). A second reason is due to the different hazard presented by these patients. Agitated delirium in intubated patients is rarely a critical problem because the dangerous agitation can be easily treated with standard sedation (propofol, midazolam lorazepam...). Oppositely, higher risk of respiratory depression limits treatment in non-intubated subjects.

We wanted to investigate the problem of agitated delirium in non-intubated patients because it represented one of the main therapeutic challenges in our ICU.

Strictly speaking, the treatment of delirium with dexmedetomidine could be seen as an «off-label» indication. Off-label drug use refers to the prescription of licensed drugs for clinical indications or in a manner different from that approved by the regulatory authorities and thus not included in the approved labeling for the agents. Use of drugs for a clinical indication, in a patient population, through a route of administration, or with a dose not specified in the FDA-approved labeling can all be considered off-label (7). the off-label use of drugs is very common in pediatrics and oncology (between 20% and 60% according different studies) (8). Off-label use does not necessarily mean a lack of evidence demonstrating the efficacy and safety of the used agent; but the supporting evidence for different off-label indications may vary considerably both in extent and quality (9). These reasons explain the non-randomized design of our study. Our Committee on Bioethics and Human Research did not authorize our proposal of a controlled, randomized, double-

blinded trial comparing haloperidol, dexmedetomidine, and placebo in these patients. After analyzing our results, we believe that, considering that we did not observe significant complications with dexmedetomidine, a further, larger, randomized, double-blinded trial would be sufficiently safe.

The second comment refers to three of reviewers assertions.

First point focuses on the lack of information about the effectiveness of dexmedetomidine as first-choice agent. As we explained in the article, the ethical constraints prevented its use. However, today, dexmedetomidine is authorized as first-choice agent for agitated delirium in our hospital. Currently, we accumulating the experience of more than a thousand patients treated with this drug. We recorded 5% of therapeutic failures and 8% of several adverse effects only.

The second point is the lack of inclusion of patients with hypoactive motoric subtype of delirium. We do not include them because our primary endpoint was treat especially dangerous agitation rather than prevent and resolve delirium. The advantages to prevent the non-agitated delirium are obvious, but were outside the scope of our research. The new evidence suggests that dexmedetomidine may have a preventive use of delirium (10,11) but readers should remember that this is another off-label indication that should be confirmed conclusively in the future research.

The third point responds to the haloperidol doses utilized in our work. These were much higher than those recommended in psychiatric patients. However, it should be noted that the greater risk involved in agitation justifies that the ICU guidelines recommend intravenous daily doses from 26 (12) to 1,540 mg (13). The doses of haloperidol necessary to relieve agitation in the ICU may be higher in comparison to non-ICU settings. Unfortunately, there are little data in the way of formal pharmacological investigations to guide dosage recommendations in the ICU. In our daily practice, infusions of this agent at daily dosage higher than 30 mg induce oversedation at a rate near 35%. For all these reasons, the committee that supervised the study decided to establish 30 mg as maximum daily doses of in both bolus and infusion.

The third and final comment is addressed to provide some reflections about the future direction of the research on ICU delirium. Sometimes (though less than we would like in an ideal world), the synergy between pharmaceutical industry and independent researchers benefits our patients. This could be the case of dexmedetomidine. As explained in the article, our study was carried out with funds from our service without any external input (our hospital is a non-profit organization). In fact, the pharmaceutical laboratory did not know neither the design nor the results until after publication. In our opinion, today the laboratory does not appear to recognize that the real target for dexmedetomidine is agitated and non-intubated ICU patients. For this indication, both haloperidol and standard ICU sedatives (propofol, midazolam lorazepam...) presents as great disadvantage a significant risk of respiratory depression. If the industry promote their collaboration with researchers under ethical premises and respect for the rigor of future studies, we all (clinicians, patients and the industry itself) could be benefited.

In conclusion, we believe that the interest in off-label uses of dexmedetomidine could promote future researches on agitated delirium that it remains one of the challenges of critical medicine.

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Footnote

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Parker RO, King AB, Hughes CG, *et al.* Dexmedetomidine for the treatment of hyperactive delirium refractory to haloperidol in non-intubated patients. J Thorac Dis 2016;8:E596-8.

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