

## Reply

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## Reply to the Letter to the Editor “Does Remifentanil Have a Place for Sedation in the Case of Endotracheal Intubation or Minimally Invasive Surfactant Therapy in Neonates?”

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Dear Sir,

We welcome the interest shown by Chollat et al. [1] in our article on remifentanil as an induction agent for the INSURE procedure in preterm neonates [2]. We thank the authors for their critical feedback from their experience in the field. Based on our own experience and on the available literature, we would like to comment on some of these critical comments.

The authors state that remifentanil has become an agent used for sedation and analgesia for tracheal intubation or minimally invasive surfactant therapy (MIST). Over the past decade several articles have appeared in the literature on the use of remifentanil for endotracheal intubation, either as sole medication or in combination with other drugs [3–6]. Also, one article studied the effect of remifentanil during the Intubation-SURfactant-Extubation procedure [7]. However, to the best of our knowledge no studies have yet appeared in the literature investigating the efficacy and safety of remifentanil during MIST.

We studied the efficacy and safety of remifentanil during INSURE [2]. In their comment Chollat et al. [1] refer to the MIST procedure on several occasions. We

would like to point out that INSURE and MIST are different procedures. During INSURE an endotracheal tube is placed and invasive ventilation is applied for a short period of time. Although recovery of the respiratory drive should be quick, completely maintaining the respiratory drive is less important. MIST was developed to prevent any artificial ventilation during surfactant administration. While the patient is spontaneously breathing on noninvasive respiratory support, a small catheter is placed through the vocal cords and surfactant is administered. So maintaining a sufficient respiratory drive is a key element in the MIST procedure. These different principles could warrant different levels of sedation.

According to the authors it seems inappropriate to reach a stage of general anesthesia using an opioid alone. We completely agree with this statement. The purpose of administering premedication before endotracheal intubation, also for the INSURE procedure, should be to reach a level of sedation and analgesia enough to blunt the stress response, reduce the physiological abnormalities that can accompany this

stress response, facilitate the procedure, and reduce the potential for airway injury [8–13]. In order to achieve these goals, a certain level of sedation should be achieved. There is no uniform definition of sufficient sedation before intubation and there are no validated methods to measure the degree of sedation. The sedation score we used should, in our opinion, adequately reflect the degree of sedation necessary to achieve the goals of premedication before endotracheal intubation. However, this score is yet to be validated.

Studies that evaluated remifentanil as single agent before endotracheal intubation used doses ranging from 1 to 3 µg/kg [3–5, 7]. Chollat et al. [1] concluded that the doses used in these studies provided a good quality of sedation. These studies did indeed find no significant differences in the total duration of intubation time and the number of attempts for successful intubation between the remifentanil group and the control groups. Unfortunately, no difference between remifentanil and other combinations of drugs does not indisputably indicate adequate sedation in the remifentanil group. It can just as well mean

that the sedation is as bad as in the control groups. All studies do not explicitly report on the quality of sedation.

Several other parameters can give an indication about the quality of sedation, for example, the number of attempts and intubation conditions. In the study by Choong et al. [3] using 3 µg/kg of remifentanyl in 60 s, self-reported intubation conditions rated by the intubator on a 7-point Likert scale were fair to poor in 25% of cases. Besides this, 3 patients received additional succinylcholine for reasons other than chest wall rigidity. Avino et al. [4] administered 1 µg/kg remifentanyl in 60 s and intubation conditions were poor in 31% of patients. Also, 4 patients were excluded from the analysis because they needed more than 2 intubation attempts. Although there could be other explanations, these data could also reflect an insufficient degree of sedation. Only Welzing et al. [7], evaluating remifentanyl during INSURE, reported excellent or good intubation conditions in all patients. Although 29% of patients needed a second intubation attempt,

the authors mentioned that inadequate sedation was never the reason for failed attempts.

Taking this into consideration, the ineffectiveness of remifentanyl in our study seems to possibly be in contrast with these previous studies. Chollat et al. [1] suggest that a short time frame to allow for drug effect could be the possible cause. As described in the methods section of our report, the sedation score was performed after remifentanyl infusion and if inadequate, the score was repeated after 30–60 s, before a subsequent dose was administered. This leads to an interval between remifentanyl doses of about 90–120 s, enough to allow for drug effect based on the known fast onset of action of remifentanyl.

Remifentanyl has a rapid onset and end of action, and almost immediate recovery of the clinical effect after interruption of administration. Thus, it has a short context-specific half-life with a short elimination time that is not influenced by the infusion time with no cumulative effects [14]. Based on these pharmacokinetic character-

istics, assuming cumulative dosing in patients receiving multiple doses seems inappropriate, and each dose should be accounted for on its own. Even if speaking of cumulative dosing should be justified, the cumulative doses used in our study are not that much higher than those used in previous studies administering a single dose [3–5, 7].

Finally, we would like to briefly address the issue of chest wall rigidity. We definitively agree with Chollat et al. [1] that the incidence of chest wall rigidity in our study was much higher than in previous studies. We attribute this higher incidence completely to the fast infusion rate of remifentanyl we used in our study, which was twice as fast as in previous studies. Therefore, in our opinion it is justified to hold on to our conclusion that with an infusion rate of 30 s, remifentanyl carries an unacceptable high risk of side effects. We do agree that when using slower infusion rates, remifentanyl seems to be much safer. We also agree that remifentanyl might be a feasible drug for INSURE or MIST, if used appropriately.

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