Opioid Tolerance or Opioid Withdrawal?

To the Editor:

We thank Kim *et al.* for their recent work examining the effect of intraoperative remifentanil on postoperative analgesia in children.[1] Certainly, the pharmacokinetic profile of this potent opioid is attractive in modern anesthetic practice, and a thorough understanding of the principles behind tolerance, hyperalgesia, and withdrawal of remifentanil are critical for its safe administration.

The authors correctly define acute tolerance as a "progressive decrease in response to a drug which can be overcome by increasing the dose of the drug." They conclude that remifentanil doses of 0.6–0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$ induce acute tolerance for 24 h after surgery based on evidence of increased postoperative fentanyl consumption. This conclusion does not seem entirely accurate based on the data presented.

The study methodology called for fixed dosing of remifentanil with abrupt discontinuation of the infusion when the surgical procedure ended. Despite this fixed dosing, their figure 1 demonstrates no hemodynamic evidence of waning remifentanil effect, and the article provides no evidence of increased volatile anesthetic requirements with time. Therefore, the requisite decreased response to or increased drug requirement for remifentanil remains unproven, and the occurrence of acute tolerance cannot be confirmed.

Another explanation for the authors' observations would be withdrawal from remifentanil, especially considering the study methodology called for abrupt discontinuation of the experimental infusion at the end of surgery. Administration of a bridging dose of opioid, an established technique for mitigating the effects of remifentanil withdrawal, was not allowed in this protocol.[2] In fact, patients did not receive any other analgesia until emergence from their anesthetic. Unfortunately, the authors did not collect clinical endpoints specific to opioid withdrawal including agitation or hemodynamic changes in the immediate postoperative period, and no consideration of this diagnosis is obvious in the article.

Furthermore, figure 2 of the article demonstrates that pain scores were only significantly different between the control and intervention groups during the first postoperative hour. Unfortunately, the authors only presented total fentanyl consumption at the 24- and 48-h time points; therefore evaluation of fentanyl consumption at earlier time points cannot be derived from the article. It is entirely feasible that opioid requirements were really increased only early in the postoperative course for those receiving remifentanil until acute withdrawal had resolved *via* infusion of fentanyl.

Although the authors argue that subanesthetic doses of volatile anesthetic have little effect on analgesia or hyperalgesia, they overlook the potential for continued postoperative sedation in the control group as a result of higher volatile anesthetic exposure during the intraoperative period. Data regarding postoperative sedation are not presented in the article. This potential confounder could also account for the finding of lower pain scores in the control group during the first postoperative hour.

In 2010, this same group published results of parent- or nurse-controlled analgesia in the same surgical population and used these data as the basis for their power analysis in the current article.[3] For patients receiving only fentanyl for postoperative analgesia, typical fentanyl consumption was 18.1 ± 4.6 $\mu g \cdot kg^{-1} \cdot day^{-1}$ at 24 h and 16.6 ± 5.5 $\mu g \cdot kg^{-1} \cdot day^{-1}$ at 48 h. In the current study, subjects randomized to receive the highest remifentanil dosing strategy (0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$) actually consumed *less* fentanyl than historic controls (17.8 ± 3.6 $\mu g \cdot kg^{-1} \cdot day^{-1}$ at 24 h, 9.2 ± 2.1 $\mu g \cdot kg^{-1} \cdot day^{-1}$ at 48 h). This inconsistency further highlights that the observed differences in postoperative opioid consumption were probably related more to the abrupt discontinuation of and subsequent withdrawal from remifentanil rather than acute tolerance to μ-agonists.

Finally, we question the approval of such a research protocol in a population of subjects that cannot themselves consent for participation. Although we understand the need to conduct research in children, this protocol seems to put both control and experimental subjects at risk of significant pain. The authors acknowledge that ureteroneocystostomy is associated with "moderate to severe pain," yet they allowed the control group to effectively emerge with no analgesic component to their anesthetic. Although their pain scores were superior in the first postoperative hour, the potential for pain should have mandated some analgesia at emergence within the experimental protocol as these authors have reported previously.[3] Furthermore, the phenomenon of withdrawal and hyperalgesia from remifentanil is well-documented, yet the absence of a bridging dose of opioid coinciding with remifentanil discontinuation placed those children in the experimental group at risk of both significant pain and the physiologic effects of acute opioid withdrawal.[4] Future evaluations of the effects of remifentanil should abandon this methodology as it is inappropriate for those unable to personally consent to experience significant pain.

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References

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(Accepted for publication July 22, 2013.)

In Reply:

We would like to thank Drs. Youngblood and Harbott for their interest in our article[1] and for their valuable comments. In their letter, they voiced concerns about the methodology and interpretation of our results. At first, we have to mention the issue on the discrepancy in postoperative fentanyl consumption between current study and our historic control[2] because Drs. Youngblood and Harbott believe that inconsistency in opioid consumption is one of the important evidences of withdrawal from remifentanil. As we had briefly described in the method sections of both studies, the surgical procedures were different from each other; the one in the former study was open ureteroneocystostomy *via* a 4–5 cm of Pfannenstiel incision (open Cohen technique), whereas the one in the current study was laparoscopic Cohen surgery under pneumovesicum. Although current laparoscopic technique has not yet achieved widespread acceptance in comparison with open procedure, minimally invasive surgical procedures have been increasingly replacing their open surgery counterparts in the field of pediatric urology.[3] As laparoscopic ureteroneocystostomy usually requires only three of 3–5 mm of trocar entries, it has several advantages, including improved cosmesis and relatively reduced bladder trauma. Postoperative pain, of course, will be expected to be less than that of open procedure. Based on our empirical observations, the setting of patient-controlled analgesia in the former study has higher rates of background infusion by 25% than that in the current study (0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl *vs.* 0.20 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl). Furthermore, if the children seemed to be consistently uncomfortable with initial settings, the fentanyl dose in the former study was doubled (56.3% of children were given "double fentanyl" during the first postoperative 48 h), whereas which was not needed in the current study. In addition, the age populations of both studies are considerably different as well; 0.5–2 yr *versus* 1–5 yr. As there has been no established pharmacokinetic/pharmacodynamic model of fentanyl especially in pediatric population, it is plausible to say that efficacies of μ-opioid agonists in children can be inferred by extrapolating from generally accepted remifentanil model. Minto *et al.*[4] identified that age is a significant covariate of EC_{50} in remifentanil model at the rate of 1.0–8.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (EC_{50} = 19.0 – 0.148 × Age). With increasing age, EC_{50} decreased, suggesting that as age decreases, the potency of μ-opioid agonist decreases. Therefore, it seems unreasonable to assert remifentanil withdrawal based on the discrepancies seen in fentanyl consumptions between two apparently different studies.

Another important issue that Drs. Youngblood and Harbott had brought out is bridging dose of analgesics. We agree with their opinion in that absence of long-acting opioids may place those children at risk of postoperative pain. However, we wish to point out that the most prominent feature of pain after ureteroneocystostomy is moderate-to-severe intermittent pain due to not only surgical incision but also bladder spasms. Bladder spasm is a common adverse event after surgeries that involve bladder dissection. As the nature of pain is mainly intermittent, the patient-controlled analgesia response to postoperative pain is both quick and efficient. We regarded residual depressant effects of long-acting opioids as particularly harmful to the convalescent children after laparoscopic ureteroneocystostomy because the risk of laryngeal edema is higher than that of open procedure, owing to surgical positioning and prolonged operative time. Therefore, all children received patient-controlled analgesia for postoperative pain control rather than a bolus injection of long-acting opioids as the latter when administered just before or after the end of surgery may induce severe, delayed respiratory depression.[5] Moreover, as children undergoing urologic surgery are not infrequently combined with various concealed anomalies, we respectively do not believe that routine use of long-acting opioid at emergence is always warranted, even in the absence of current trial. However, basal infusion of fentanyl for patient-controlled analgesia might attenuate the differences in the postoperative cumulative fentanyl consumptions in our study, although we of course considered that basal infusion would make children more comfortable.

According to current guidelines of opioid dosage,† the recommended dose of remifentanil used to maintain sevoflurane anesthesia in children aged 1–12 yr is 0.05–1.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In adults or adolescents, a remifentanil infusion dose of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is associated with the development of acute tolerance. In small children, precise dosage and duration of remifentanil that is associated with tolerance had not been determined, and data were fragmentary and conflicting. Despite our current result, we cannot conclude that administration of remifentanil at a dose of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ does not cause acute tolerance after any duration of infusion. As tolerance to opioid is dose-dependent,[6] part of the explanation for no hemodynamic evidence of waning remifentanil effect seen in our result may be related with age-related pharmacodynamic difference of μ-opioid agonist and possibly with discrepancy of infusion duration. We do not disagree with Drs. Youngblood and Harbott that our study was underpowered to assess opioid withdrawal thoroughly, and acute tolerance

† Available at: http://www.drugs.com/dosage/remifentanil.html. Accessed July 18, 2013.