Midazolam for Anxiolysis and Postoperative Nausea and Vomiting Prophylaxis: Can We Kill Two Birds with One Stone?

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Postoperative nausea and vomiting (PONV) remains the most common anesthetic-related complication in today's perioperative environment and one of the most feared outcomes by patients before surgery.[1] With better understanding of the multiple receptor pathways involved in the pathogenesis of PONV, we are now able to optimize the antiemetic prophylaxis in high-risk patients by using a multimodal approach that targets several different receptor systems.[2] However, in high-risk patients, studies using a multimodal approach incorporating total IV anesthesia with propofol and a combination of 2 or 3 antiemetics working at different receptors have reported a PONV incidence of approximately 20%.[2,3] Therefore, the research is ongoing to find additional strategies that could be used to further reduce the incidence of PONV.

Midazolam is widely used as an anxiolytic in both adult and pediatric patients. Some studies published >2 decades ago have suggested that benzodiazepines, including midazolam, might have antiemetic properties in the perioperative period[4] as well as in the management of chemotherapy-induced nausea and vomiting.[5,6] So does this widely used anxiolytic provide a clinically useful antiemetic effect?

In this issue of *Anesthesia & Analgesia*, the authors of 2 meta-analyses investigated the perioperative use of midazolam as a prophylactic antiemetic. The meta-analysis by Grant et al.[7] included 12 studies, whereas Ahn et al.[8] included 4 additional studies (2 that added midazolam to a postoperative patient-controlled analgesia regimen[9,10] and 2 tracked PONV as a secondary outcome that was not clearly noted in the abstract).[11,12] The 12 studies included by both meta-analyses investigated the preoperative IV administration of midazolam in doses ranging from 40 to 75 μg/kg, whereas 2 of the studies included a dose 30 minutes before the end of surgery (1 of which also dosed midazolam at induction). All studies compared midazolam with placebo except for 3 studies included in both meta-analyses that studied the addition of midazolam to another antiemetic. The outcomes of both meta-analyses were postoperative nausea, postoperative vomiting, and PONV in the first 24 hours. In addition to the overall 24-hour analysis, the study by Ahn et al. also parsed the effect of midazolam into early (0–6 hours after surgery) and late (6–24 hours after surgery) time periods. Both meta-analyses were well conducted and suggest a substantial 38% to 55% reduction in the risk of overall PONV with the perioperative administration of midazolam and also showed a benefit in both early and late time periods. Those results were consistent in a number of subgroup analyses and suggest that the beneficial antiemetic effect was seen irrespective of dose or time of administration of midazolam (preoperative/at induction or at the end of surgery), gender, type of surgery, anesthetic technique, and whether PONV was a primary or secondary endpoint in the included studies. It is certainly reassuring that consistent results were found within the extensive subgroup analyses performed in both studies. However, a number of issues need to be carefully assessed to accurately evaluate the data presented in these articles.

The first issue that needs to be addressed is the risk of publication bias. This refers to the fact that clinical trials with positive or statistically significant results are more likely to be published than trials with negative or nonstatistically significant findings.[13] Because a meta-analysis includes an aggregate of published clinical trials, the pooled results might overestimate the true effect of the studied intervention when it does not include the unpublished negative studies. Only the meta-analysis by Ahn et al. assessed for the presence of publication bias and indeed reported that visual inspection of the funnel plots as well as the results of the Egger test indicate that there was significant funnel plot asymmetry suggesting a possible risk of publication bias for the outcomes examined in the meta-analysis. They followed this up by adjusting for the publication bias using the trim and fill method and recalculated the relative risks for 5 different outcomes (early and late nausea/vomiting and need for rescue antiemetics). This adjustment brings the relative risk associated with midazolam on postoperative nausea and postoperative vomiting in the first 6 hours closer to 1 (0.95 and 0.84, respectively) with a wide 95% confidence interval (0.38–2.34 and 0.41–1.67, respectively). The effect was still statistically significant for overall postoperative nausea and postoperative vomiting (0–24 hours after

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surgery) as well as need for rescue treatment. However, it is important to note that this meta-analysis also included 2 studies that investigated the use of midazolam when added to postoperative patient-controlled analgesia. Most other studies in the meta-analysis used midazolam before the start of surgery rather than a postoperative infusion. Therefore, it is not clear whether similar results are obtained if the adjustment for publication bias included only studies using preoperative administration of midazolam, which is used most commonly in current practice. Furthermore, although the results were still statistically significant for overall postoperative nausea and postoperative vomiting, significant caution is needed when interpreting the results of the trim and fill method because it is based on assumptions that might not be valid and uses imputed intervention effect estimates, which reduce the uncertainty of the summary intervention effect.[14] However, it is important to remember that publication bias is only 1 of the reasons for funnel plot asymmetry. A contour-enhanced funnel plot can help differentiate whether funnel plot asymmetry is attributable to publication bias or other reasons,[15] but such a plot was not evaluated.

The second issue that needs to be highlighted is the side effect profile of midazolam. Indeed, one might be reluctant to use midazolam for the sole purpose of PONV prophylaxis, especially in the ambulatory setting and in elderly patients,[16] because of concerns about sedation that might lead to a prolongation of postanesthesia care unit (PACU) stay. Both meta-analyses examined sedation and reported no statistically significant increase in the risk of sedation or significant sedation with midazolam. The summary estimates in both studies had very wide 95% confidence intervals (relative risk, 1.91 [0.58–6.29] and 1.33 [0.65–2.71]). What we can therefore appropriately conclude is that the results did not show a statistically significant increased risk of sedation or significant sedation with midazolam, but the imprecision of the pooled estimate does not rule out a clinically relevant 3- to 6-fold increased risk of sedation with perioperative midazolam administration. Grant et al. also stated that 2 of the included studies reported increased sedation with midazolam. This may be reason enough to cause a significant reduction in rescue antiemetic administration. However, does this translate to a clinically relevant impact on the patients' recovery? Grant et al. reported no prolongation in the duration of PACU stay with the use of midazolam in their meta-analysis, although they did not indicate the number of studies reporting this outcome. A previous meta-analysis also reported no prolongation in the duration of PACU stay with midazolam premedication, but the authors noted that the methodological quality of included studies was poor.[17]

These 2 meta-analyses show a substantial and significant prophylactic effect of midazolam on PONV with a number needed to treat of 3 to 4. The half-life of midazolam is estimated to be approximately 2 hours[18] and can be twice as long in elderly patients,[19] which may lead to a prolonged effect (and sedative side effect) in this population. Midazolam is effectively cleared from the body 10 hours after administration, which would coincide with the start of the period of late PONV reported by Ahn et al. The results of those meta-analyses therefore suggest that midazolam might have antiemetic effects that outlast its presence in the body, although this may be impacted in part by the inclusion of studies using postoperative infusions of midazolam. The mechanism of the antiemetic effect of midazolam is not entirely clear. Some suggested mechanisms include decreased dopaminergic activation at the chemoreceptor trigger zone as well as reduced 5-hydroxytryptamine release by binding to the γ-aminobutyric acid benzodiazepine complex.[4] It is also not clear whether the antiemetic effect is related to the anxiolytic effect of midazolam; although earlier studies suggested that preoperative anxiety may be a risk factor for PONV, it was subsequently shown to be a very weak risk factor that did not improve the discriminating power of PONV scoring systems.[20]

What then is the take-home message for the practicing clinician? The antiemetic effect was seen when midazolam was administered preoperatively or at induction of anesthesia as well as at the end of surgery. This beneficial effect also appeared to be comparable between low doses (<0.05 mg/kg) and high doses (>0.075 mg/kg) although there were no head-to-head comparisons between the 2 doses. Therefore, administration of midazolam as an anxiolytic also seems to reduce the risk of PONV. Although the meta-analyses did not compare midazolam with other antiemetics, limited data suggest that it might have similar efficacy to ondansetron,[21,22] but more data are needed to compare its efficacy with that of other antiemetics. Future studies should also explore the interaction between midazolam and other prophylactic antiemetics, whether a regimen incorporating midazolam with another antiemetic is comparable to a regimen including 2 antiemetics, whether it offers an additional benefit to a multimodal approach incorporating combination antiemetic therapy and total IV anesthesia with propofol, and closely assess sedation and impact on patient recovery.

In conclusion, the meta-analyses by Grant et al. and Ahn et al. suggest that midazolam has a clinically relevant antiemetic effect. However, these results should be interpreted with caution in the light of possible publication bias and the inability to exclude a clinically relevant increase in the risk of sedation. Additional work is needed before we confidently use midazolam solely for its prophylactic antiemetic effect. Meanwhile, we should continue to use midazolam as appropriate for its anxiolytic effect; we might be killing 2 birds with 1 stone!

DISCLOSURES

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