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LETTER

Methodological Concerns Regarding ED95 Estimation and Outcome Interpretation in the Remimazolam Dose-Finding Study for HIFU Ablation [Letter]

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Dear editor

We read with interest the dose-finding study by Wei et al on the ED50 and ED95 of remimazolam combined with sufentanil for HIFU ablation. The authors are to be commended for addressing a clinically relevant question in procedural sedation. However, we would like to raise several methodological points that we believe deserve further discussion.

First, we are concerned about the analytical approach used to estimate ED95. The study employed Dixon's up-and-down sequential method for dose allocation and then applied probit regression to derive both ED50 and ED95. As has been pointed out in the literature, the up-and-down method is primarily designed to estimate the median effective dose (ED50) and may not be reliable for estimating high-percentile effective doses such as ED90 or ED95.[1,2] The dose distribution generated by this sequential design clusters around the ED50, providing relatively little information about the tails of the dose-response curve. Using probit regression on such data to extrapolate ED95 may therefore yield estimates that are heavily model-dependent and potentially unstable Several recent dose-finding studies have adopted isotonic regression or centered isotonic regression for ED95 estimation when using up-and-down designs. We would be interested to know whether the authors considered such alternative approaches and, if so, how the results compared.

Second, the unusually wide confidence interval for ED50 raises questions about estimation precision. The reported ED50 was 0.064 (95% CI: 0.025–0.086) mg/kg/h. This 95% confidence interval spans more than a two-fold range, with the lower bound being less than one-third of the point estimate. In up-and-down designs, such wide intervals typically suggest either substantial inter-individual variability or an insufficient number of crossover points.[1] While the authors stated that 40 patients were enrolled to achieve at least 10 crossover points, the actual number of crossover points was not explicitly reported. We would appreciate clarification on this point, as the reliability of the ED50 estimate depends critically on whether a sufficient number of reversals was observed.

Third, the interpretation of BIS values during remimazolam sedation merits reconsideration. The authors observed that despite Ramsay Sedation Scale scores indicating adequate clinical sedation (Ramsay ≥2), BIS values remained relatively elevated (70.9 ± 7.9 to 86.0 ± 7.2) throughout the procedure. They attributed this to electromyographic interference and the lower sensitivity of BIS to benzodiazepines. However, the study did not report a formal correlation analysis between BIS and Ramsay scores. Previous research has shown that BIS has limited accuracy in detecting

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sedation depth when benzodiazepines are used, and that the correlation between BIS and clinical sedation scales may diminish over time.[3] Without presenting the actual correlation coefficients or a scatterplot, the conclusion that "BIS values during remimazolam sedation should be interpreted with caution" remains insufficiently supported by the data presented.

Fourth, we note that the conclusion regarding multimodal antiemetic strategies may be premature. The study found a 30.0% incidence of postoperative nausea and 22.5% of vomiting despite routine prophylaxis with 8 mg ondansetron. The authors then recommended exploring multimodal antiemetic regimens. However, as a dose-finding study without a control arm, this investigation was not designed to evaluate antiemetic efficacy. The observed PONV rates in this all-female cohort-a well-established high-risk population-may simply reflect the baseline risk rather than inadequate prophylaxis.[4] The post hoc stratified analysis in Table 6,[5] based on median cutoffs, was also underpowered to detect differences given the sample size originally calculated for dose estimate on. We suggest that the authors acknowledge these limitations more explicitly and avoid over-interpreting secondary safety outcomes.

We wish to emphasize that these observations are not intended to diminish the value of this important work. Rather, we believe that addressing these points would further strengthen the manuscript and enhance its contribution to the literature. We look forward to the authors' response.

Disclosure

The authors report no conflicts of interest in this communication.

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