Poster

[P26-4] P26-4: Central nervous system drugs (3)

Chair: Christoph Hiemke, Germany

Tue. Sep 26, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Tue. Sep 26, 2017 12:30 PM - 1:30 PM Annex Hall)

[P26-4-9] A pharmacodynamic model of midazolam-induced sedation in terminally ill adult patients

Birgit C. P. Koch[1], Linda G. Franken[2], Anniek D. Masman[3], Monique van Dijk[4], Frans P.M. Baar[5], Dick Tibboel[6], Teun van Gelder[7], Ron A.A. Mathot[8], Brenda C.M. de Winter[9] (1.Erasmus MC, 2.Erasmus MC, 3.Palliative Care Centre, Laurens Cadenza, 4.Erasmus MC - Sophia Children's Hospital, 5.Palliative Care Centre, Laurens Cadenza, 6.Erasmus MC - Sophia Children's Hospital, 7.Erasmus MC, 8.Academic Medical Centre, 9.Erasmus MC)

Keywords: pharmacodynamics, midazolam, sedation palliative care

Background

Despite being the drug of choice for palliative sedation not much is known about pharmacodynamics of midazolam in terminally ill patients. Using a previously developed a pharmacokinetic model we performed this study to characterize the pharmacodynamics of midazolam in terminally ill patients, in order to eventually develop an individualized dosing strategy.

Methods

A population pharmacodynamic analysis using nonlinear mixed effect models was performed with 941 observations from 43 patients. Depth of sedation was measured with the Ramsay sedation score. A differential odds model was used to estimate the probability for each Ramsay score given a certain midazolam concentration. The effect of the midazolam metabolites was evaluated using an additive interaction model. Patient and disease characteristics, concomitant medication and the time of day were evaluated as possible covariates. A visual predictive check (VPC) was used for model evaluation.

Results

The effect of midazolam on the sedation level was best described with an Emax equation. The EC50 value was 68.7 ug/L for a Ramsay score of 3 (drowsy or asleep responding only to commands) and 117.1 ug/L for a Ramsay score of 6 (asleep without any response). Neither of the midazolam metabolites showed an additive effect on the sedation level. Co-medication with haloperidol was associated with lower Ramsay scores.

Conclusions

We were able to accurately describe the pharmacodynamic effect of midazolam in terminally ill patients using categorical data. As expected there was large variability in the overall response to midazolam. In our model we did not find any additional effect of the midazolam metabolites. For 1-hydroxy-midazolam this is probably due to the fact that it is a formation rate limited metabolite. For 1-hydroxy-midazolam-glucuronide it may be due to its low efficacy (only 10% compared to midazolam) and the fact that patients were only sedated for a relatively short period. We found the use of haloperidol to be associated with a lower probability of sedation. This might be due to a paradoxical effect, or it can be a result of confounding by indication as haloperidol is used to treat delirium and agitation.