

Population pharmacokinetics of ketamine and norketamine in paediatric subjects undergoing analgosedation

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INTRODUCTION

Ketamine (KET) is a potent agent for paediatric sedation and anaesthesia. Its metabolite norketamine (NOR) is also pharmacologically active. Despite general effectiveness and safety, KET is associated with adverse events (AEs), such as vomiting and agitation¹. To date, the relationship between KET or NOR exposure and incidence of AEs remains unclear, but pharmacodynamic and epigenetic factors may play an important role in interindividual differences in the safety profile of KET. Among other things, micro-RNA (miRNA) might be a prognostic marker of AEs, as brain-originated vesicular miRNAs have been proposed as predictors of neurological disorders^{2,3}.

AIM OF THE STUDY

1. Characterize the pharmacokinetics of KET and NOR in paediatric subjects undergoing analgosedation.
2. Assess the potential correlation between KET and NOR exposure and incidence of AEs.
3. Explore miRNA expression patterns in subjects with and without AEs.

PK RESULTS

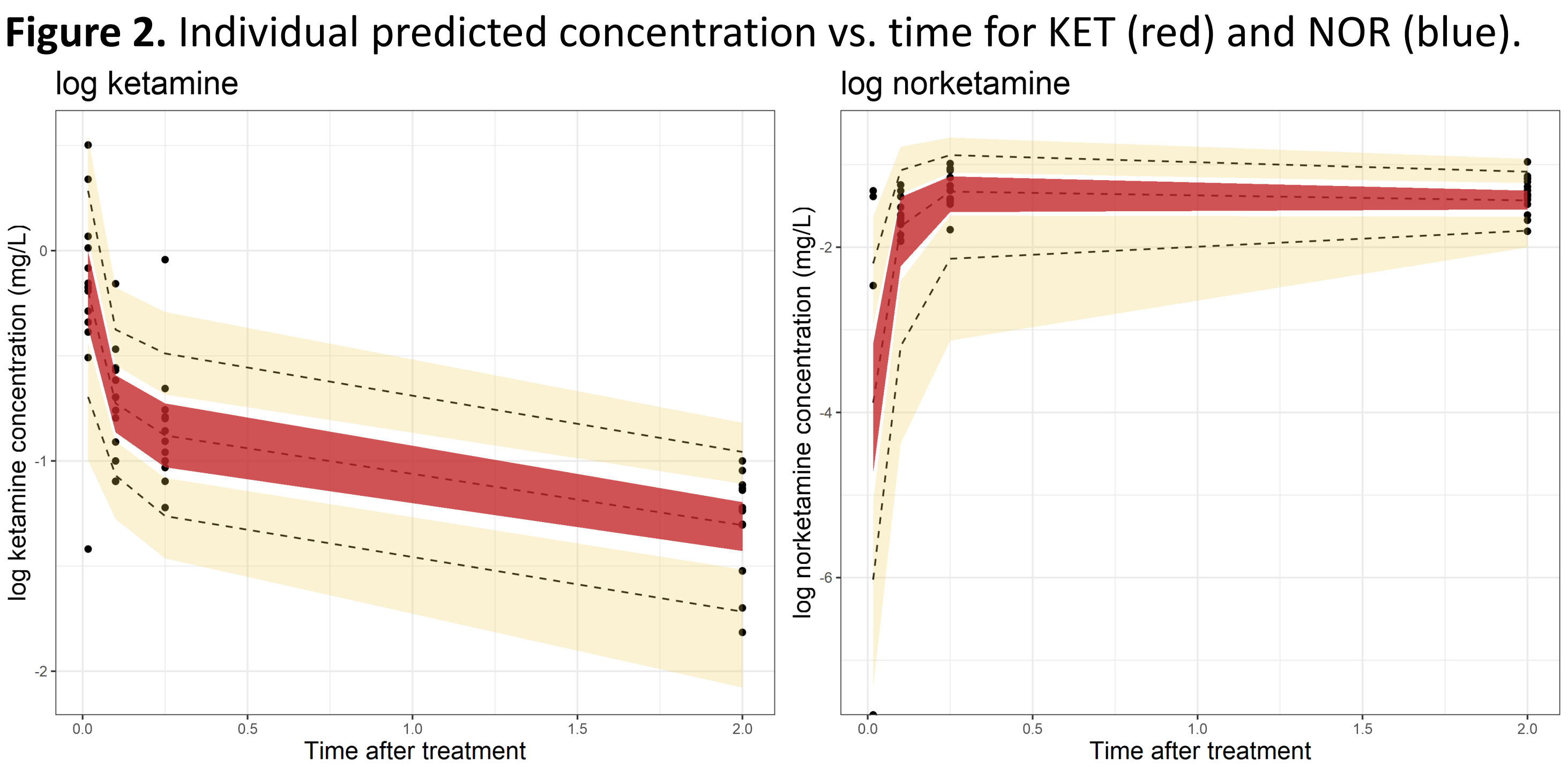
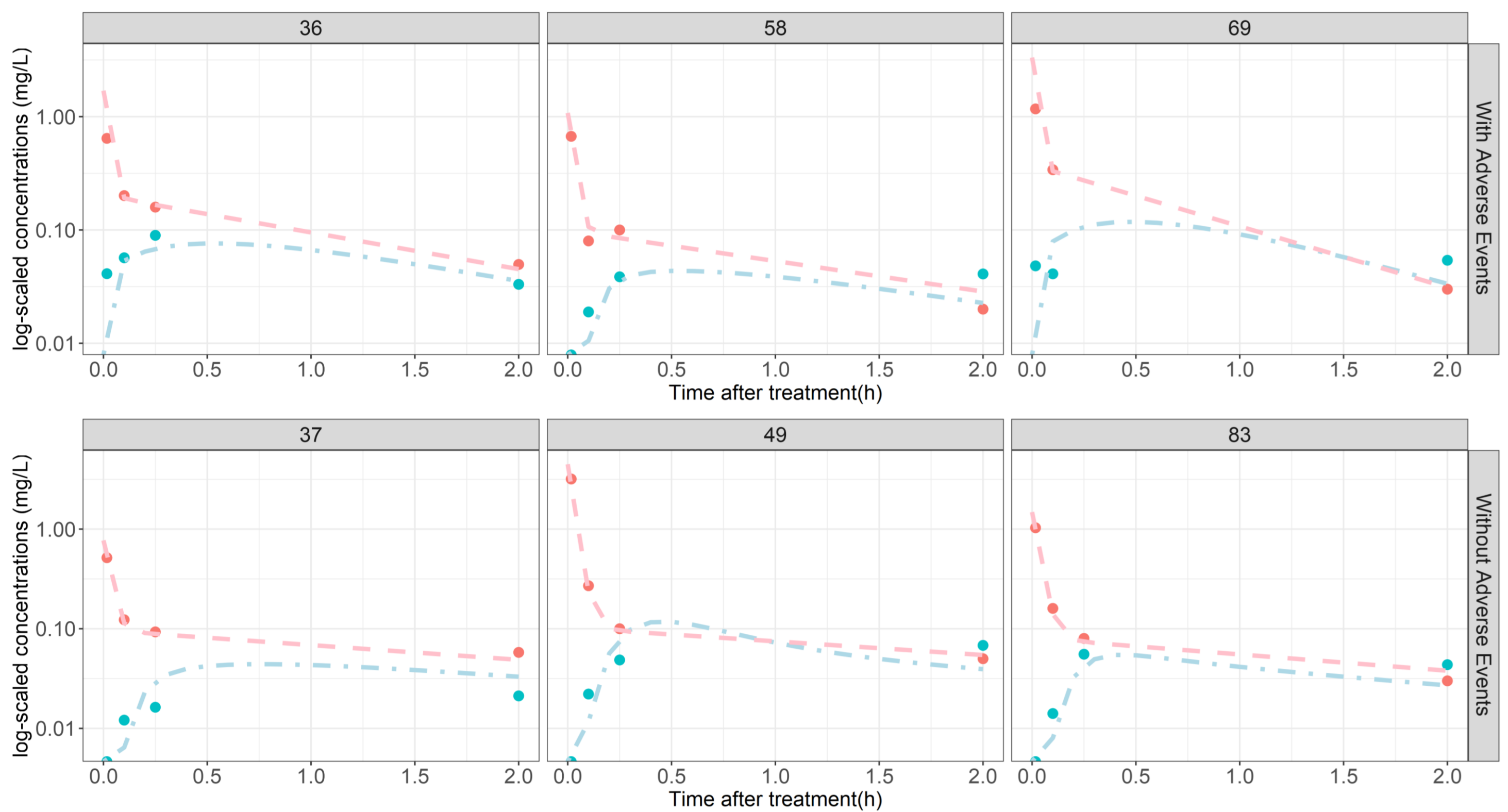


Figure 3. Visual predictive checks of KET and NOR. The model adequately described KET pharmacokinetics despite the high inter-individual variability in the formation rate of NOR.

CONCLUSION

Despite high interindividual variability in the pharmacokinetics of KET and NOR in this group of paediatric subjects undergoing analgosedation, the onset and occurrence of AEs seems to be unrelated to individual differences in systemic exposure to either moiety. These results corroborate previous findings⁵, highlighting the limitation of therapeutic drug monitoring in this clinical setting. On the other hand, the evaluation of epigenetic data reveals different patterns in patients who experience AEs. Further investigation is required to establish how these patterns vary after drug administration, and whether different susceptibility exists to noncompetitive NMDA receptor antagonists, such as KET.

METHODS

This was an investigational, multi-centre, single arm study in children receiving a single IV bolus of ketamine for analgosedation. PK samples were collected from a subgroup (N=15, age 1–17 yrs), before and at 1 min, 0.25h and 2h after the start of the infusion. Epigenetic information of 49 different types of miRNAs were obtained from a different subgroup (N=50, age 1–17 yrs). Extracellular vesicles with neural origin were isolated from blood samples² prior to treatment. miRNAs were sequenced using the Illumina platform. Population pharmacokinetic model structure and prior parameter distributions were adapted from a model by Herd *et al.*⁴. Individual POSTHOC estimates for AUC and C_{max} for both KET and NOR were derived based on the final model. Baseline epigenetic profiles were compared between subjects with or without AEs using a Wilcoxon test.

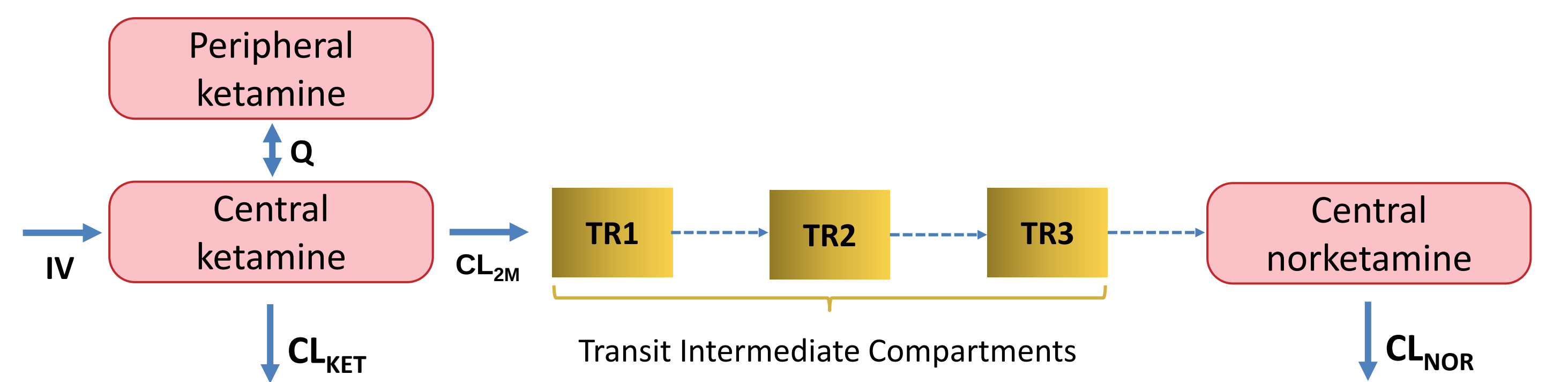


Figure 1. Model structure. CL_{2M} = metabolic clearance of KET, TR = transit CMT, CL_{KET} = KET clearance via other routes, CL_{NOR} = elimination clearance of NOR.

PK RESULTS

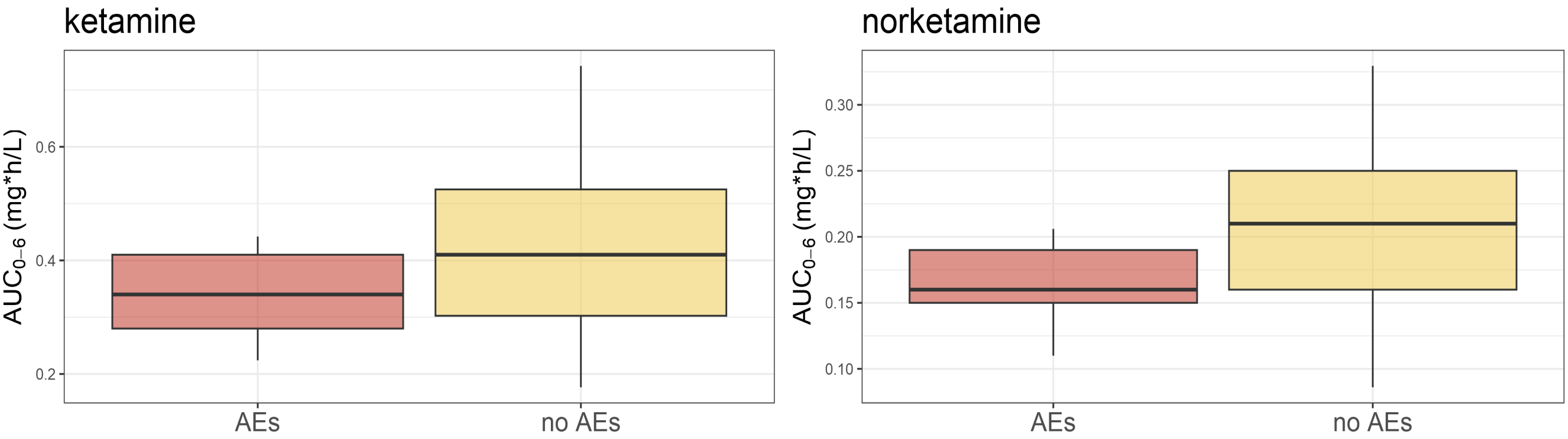


Figure 4. Predicted exposure (AUC_{0-6h}) of KET and NOR in subjects with or without AEs. No significant differences were observed between groups.

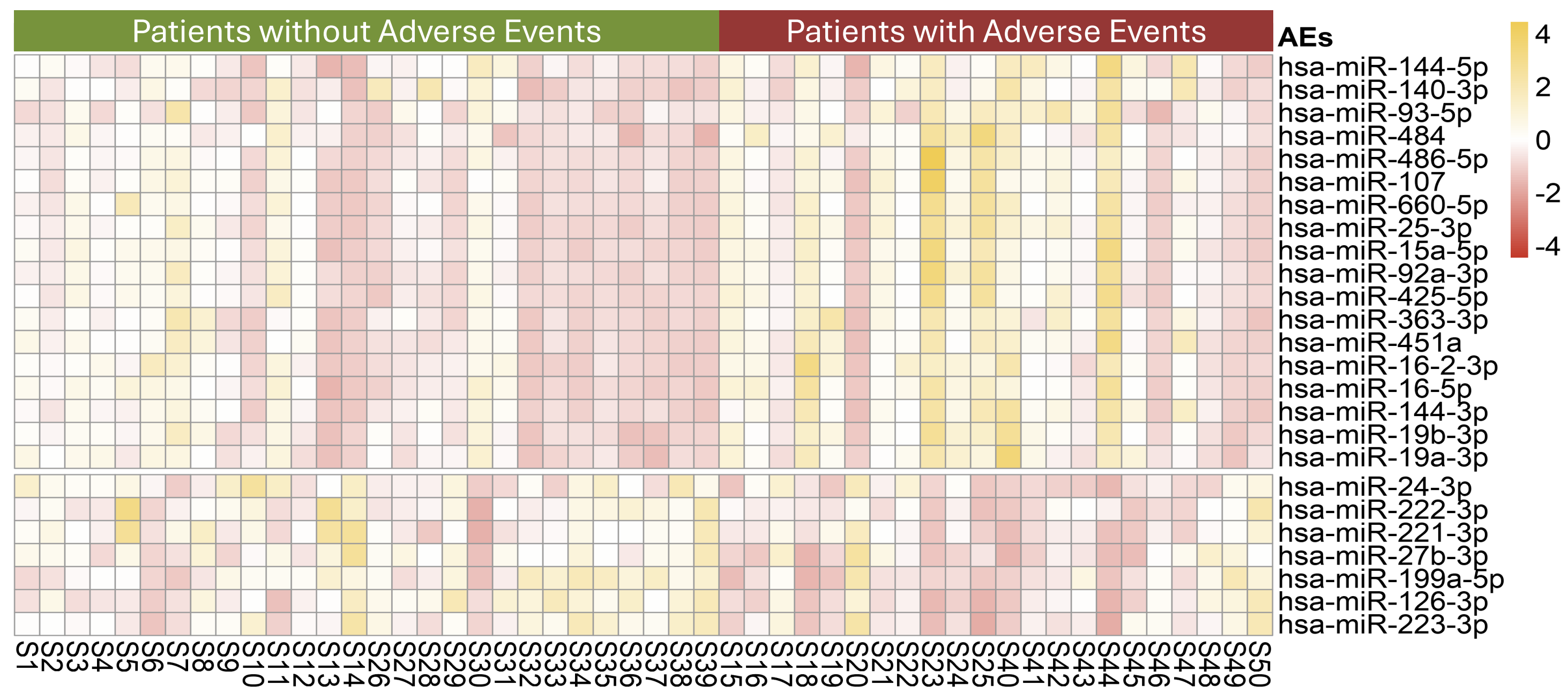


Figure 5. Expression of miRNAs. 23/49 miRNA vesicles showed significant differences ($p < 0.05$) between subjects with and without AEs. The patterns in the heatmap reveal that 18 miRNAs were up-regulated, and 7 miRNAs were down-regulated in subjects with AEs. Whilst there appears to be a potential association between miRNA expression and incidence of AEs, these data reflect gene expression patterns prior to dosing. Further research is required to establish the correlation between vesicular miRNAs and KET-related AEs.

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