

Quantification of antidepressant and sedative effect of two NMDA channel blockers, AZD6765 and ketamine, in an animal model of depression using count data



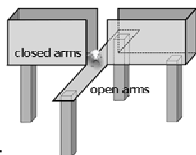
Leiden Experts on
Advanced
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Background

- Ketamine has shown effects in major depressive disorder and is known to have a sedative effect at high doses [1]
- The elevated plus maze (EPM) is a plus-shaped maze with 2 open and 2 closed arms widely used for behavioral studies in rodents
- Prenatally stressed (PNS) rats show long-lasting reduction in open-arm exploration on the EPM
- An increase in exploration of the open arms by PNS rats may indicate antidepressant effects [2].



Objective

- The aim of the current study was to develop a count model to characterize the antidepressant and sedative effects of the 2 NMDA channel blockers, AZD6765 and ketamine, on the number of open and closed entries in PNS rats

Data

- Vehicle group:
 - non-PNS rats (n=28 for AZD6765, n=47 for ketamine)
 - PNS rats (n=21 for AZD6765, n=43 for ketamine)
- Active treatment group: PNS Rats were dosed ip with AZD6765 (0.3-10 mg/kg, n=78), or ketamine (1-10 mg/kg, n=47)
- At 1 hour and 14 days, the rats were placed in the middle of the EPM and the **number of open and closed entries** were recorded for a 5 min period

Methods: Count data

- The number of entries into either closed or open arms were described using a count data modelling approach [3]
- First different distributions of the expected number of entries (λ) were investigated for the non-PNS and PNS placebo groups (Figure 1):

$$P(DV) = \frac{\lambda^{DV} \exp(-\lambda)}{DV!}$$

- Poisson

$$P(DV) = \frac{\Gamma(DV + \frac{1}{\beta})}{\Gamma(\frac{1}{\beta})} \times \left(\frac{1}{1 + \beta\lambda} \right)^{\frac{1}{\beta}} \times \left(\frac{\lambda}{1 + \beta\lambda} \right)^{DV}$$

where β is the overdispersion parameter

- With or without zero-inflation (to account for a higher probability of zero entries).

$$P(DV)_{\text{zero-inf}} = \begin{cases} (1 - P_0)P(DV) & \text{for } DV > 0 \\ P_0 + (1 - P_0)P(DV) & \text{for } DV = 0 \end{cases}$$

where P_0 is the probability of zero entries

- Intra individual variability was examined for λ and P_0

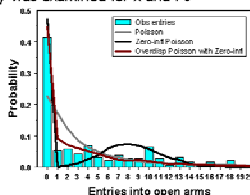


Figure 1. Number of entries into open arms for the PNS vehicle group (turquoise bars) and estimated distributions (lines).

Methods: Structural model

- A stepwise modelling approach was followed to assess the sedative, PNS and antidepressant effects

- Sedative effect: The sedative effect (SEFF) was assessed by the number of entries into closed arms (general activity).

$$\lambda_{CO} = BSL_{CO}(1 - SEFF)$$

$$P_{0CO} = TP_{0CO}$$

- PNS effect: The number of open entries was smaller and the probability of zero-entries larger in the PNS rats than non-PNS rats.

$$\lambda_{CO}(placebo) = BSL_{CO}(1 - PNS_p)$$

$$P_{0CO}(placebo) = TP_{0CO} + PNS_p$$

- Antidepressant effect: The drug reverses the PNS effect. The sedative effect on open entries was similar to the effect on closed entries.

$$\lambda_{CO} = BSL_{CO}(1 - PNS_p(1 - EFF_p))(1 - SEFF)$$

$$P_{0CO} = TP_{0CO} + PNS_p(1 - EFF_p)$$

- Different dose-effect relationships were examined for SEFF, EFF_p and EFF_c (linear, power, E_{max} and Sigmoidal E_{max})

- Models were selected based on the objective function value and/or diagnostic plots (VPC and observed vs simulated distribution of the number of entries)

Results

- An overdispersed Poisson model with zero-inflation and IIV on λ adequately described the distribution for the number of entries into open and closed arms (Figure 1)
- The sedative effect of AZD6765 and ketamine could be described by an E_{max} and Sigmoidal E_{max} model, respectively (Figure 2 and 3, Table 1). As expected there was no sedative effect on day 14. ED50 is lowest for ketamine, and the maximum sedative effect is larger for ketamine than for AZD6765 in the concentration range tested. (Figure 3)
- The antidepressant effect of both compounds could be described with a Sigmoidal E_{max} model (Figure 4 and 5). An effect was found not only for the expected number of open entries but also for the probability of zero entries
- The efficacy of the antidepressant effect of AZD6765 was higher and the duration of the effect longer than for ketamine (Figure 6, Table 2)

Sedative effect

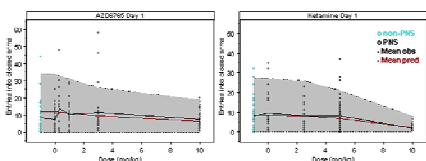


Figure 2. VPC of the number of entries into closed arms for the vehicle group (non-PNS and PNS rats) and test group (PNS rats)

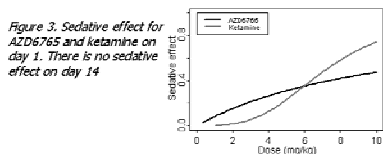


Table 1. Sedative effect parameters

Parameters (SE)	BSL _{CO}	TP _{0CO}	E _{max} *	ED50 ₅₀ [mg/kg]	σ
AZD6765	12 (0.88)	0.127 (0.027)	1	11.1 (3.59)	1*
Ketamine	9.57 (0.88)	0.247 (0.037)	1	7.22 (0.65)	3.26 (0.47)

*Fixed

PNS and Antidepressant effect

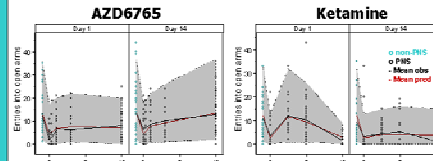


Figure 4. VPC of the number of entries into closed arms for the vehicle group (non-PNS and PNS rats) and active treatment group (PNS rats)

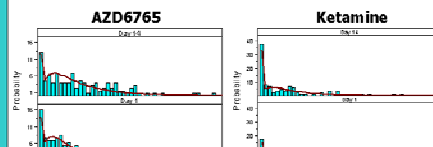


Figure 5. Observed distribution of number of entries into open arms (turquoise bars) and estimated distribution (red lines) for all dose groups and both PNS and non-PNS rats on day 1 and 14

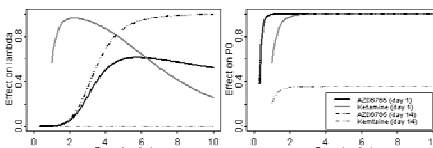


Figure 6. Combined antidepressant and sedative effect for AZD6765 and ketamine on day 1 and day 14

Table 2. Antidepressant effect parameters

Parameters (SE)	AZD6765	Ketamine
BSL _{CO}	11.4 (1.27)	9.86 (0.736)
TP _{0CO}	0.436 (0.092)	0.495 (0.054)
E _{max} * Day 1	1	1
E _{max} * Day 14	1	0
ED50 ₅₀ [mg/kg]	3.51 (0.916)	0.945 (0.207)
γ ₀ *	5	5
TPCO	0	0
PNS _p	0.423	0.588 (0.003)
E _{max} p* Day 1*	1	1
E _{max} p* Day 14*	1*	0.345 (0.182)
ED50 ₅₀ [mg/kg]	0.33 (0.072)	0.945 (0.207)
γ ₀ *	5	5

*Fixed

Conclusions & Perspectives

- A sedative effect of ketamine and AZD6765 was quantified based on the entries into closed arms. Ketamine had the highest sedative effect within the evaluated dose range
- PNS rats in the vehicle group showed reduced entries into open arms and an increase in rats having no entries compared to non-PNS rats
- Both AZD6765 and ketamine showed antidepressant effects in the PNS-EPM model through prolonged increased explorative behavior of the open arms and a reduction in rats having no entries into the open arms compared with vehicle treatment
- The potency, efficacy and time-course of compounds tested on the EPM could be well described using a count data modelling approach

Find the poster here



References

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- Wall AA and Frye CA. *Nature Protocols*. 2007;2(2):322-328.
- Stymen DJ, et al. *Epidemiol Perspect Innov*. 2006;3:3.

Disclosure

M Quirk, C Wallsten and B Ploeger are employees and C Maciag is a former employee of AstraZeneca R&D. K Bergmann, N Snelder, O Ackaert and E van Maanen are employees of LAP&P.