EUDRACT 2008-003293-18

15 JUL 2013

Final study report

(Summary of Research Findings)

Study Title: Pharmacokinetics of ketamine in infants undergoing laser therapy for retinopathy of prematurity

Name of drug: Ketalar (Ketamine hydrochloride)

Indication studied: Procedural sedation and anaesthesia in infants

Design of the study: Observational cross-sectional study to evaluate the population pharmacokinetics of ketamine in infants < 6 months old.

Name of the sponsor: Queen's University Belfast / Belfast Hospital Trust

Sponsor contacts:

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Protocol Identification number: EudraCT: 2008-003293-18; Sponsor's Protocol No.: RGHT000470; REC Ref. No.: 08/NIR01/75

Study initiation date: 17 December 2008

Study completion date: 31 May 2012

Submitted by: Prof. James McElany, Queen's University Belfast

Date of the report: 29th /May/2013

2. Synopsis/Abstract

The study applied a population pharmacokinetics approach, using nonlinear mixed effects modelling with sparse sampling, to estimate the pharmacokinetic parameters of Ketamine which is used for procedural sedation and anaesthesia in neonatal intensive care units. Dried blood spot sampling was used as the sample collection method, and suitable microanalytical methods were developed and validated to measure the concentrations in each DBS sample required for the pharmacokinetic modelling.

Ketamine is a chiral molecule and there are well established differences in both pharmacokinetics and pharmacodynamics between each enantiomer. Additionally it has an active metabolite, which is also chiral. An LC-MS/MS method was developed, validated and applied successfully for the quantification of S- and R-ketamine, and S- and R-norketamine in DBS samples collected from the patients recruited into the clinical trial. Weight was found to be the only covariate with a significant influence on either clearance or volume of distribution in this preliminary analysis. Visual examination of the plotted ratios of each enantiomer of ketamine and of norketamine suggests that the enantioselective metabolism seen in adults is also present in this very young population. It was noted, however, that the very youngest patients exhibited markedly less enantioselective metabolism. Analysis is not finalised yet and the full results of this clinical trial promise to be very interesting when available.

3. Study objectives

- To develop models characterising the pharmacokinetics of each enantiomer of ketamine in infants, including the estimation of inter-individual and residual variability
- To assess the influence of different patient co-variates on the estimated variability in pharmacokinetic parameters
- To conduct an initial visual exploratory data analysis on the chiral aspects of ketamine metabolism

- To compare the values of the different parameters in preterm neonates to those obtained in other studies and other ages.

4. Study design

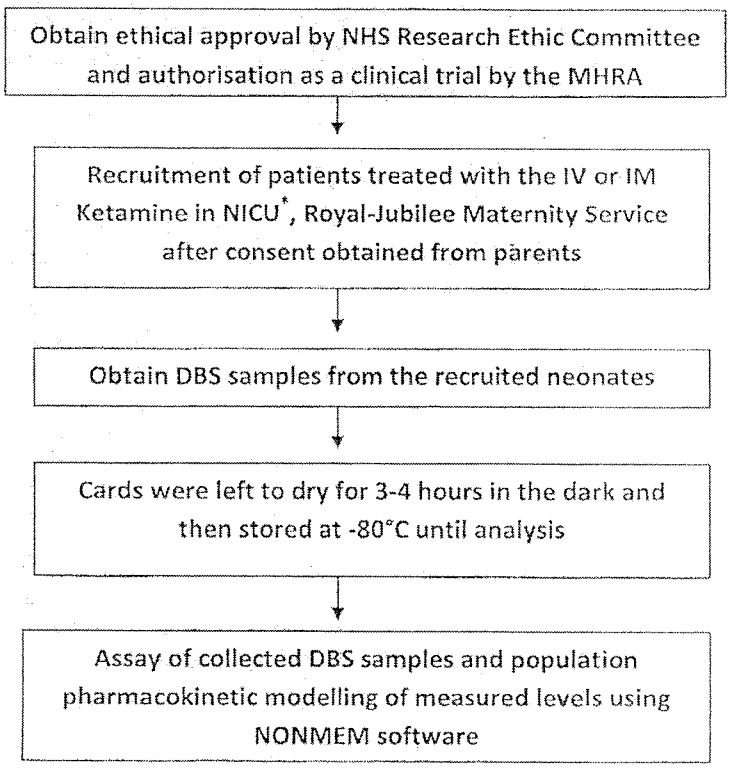

Figure 1: Study design.*NICU: Neonatal Intensiive Care Unit

5. Study results

Eighteen noenates were recruited into the clinical trial and the total number of collected DBS samples was 103. All samples have been assayes, however, PK modelling has been performed on a preliminary dataset comprised 45 observations from 8 individuals. Summary demographics for patients remaining in the final PK model are presented in Table 1.

Summary data on the number of doses and observations per patient are presented in Table 2.

Table 1: Summary of covariate information on the day of the first recorded dose in the preliminary dataset (n=8 individuals)

Covariate	Mean	Standard Deviation	Median	Minimum	Maximum
Gestational age (weeks)	28.34	5.15	26.79	24.57	40.86
Post natal age (days)	51.5	38.57	64	1	94
Post menstrual age (weeks)	35.70	5.23	37.29	27.57	41.14
Weight (kg)	1.90	0.87	1.9	0.86	3.5
Packed Cell Volume	0.385	0.090	0.345	0.290	0.549
Sodium conc	137.63	2.13	137	135	141
Potassium conc	4.475	0.5497	4.55	3.7	5.3
Urea conc	5.45	3.324	5.3	1.4	9.6
Serum creatinine (µmol/l)	37.75	16.51	38.5	18	61
Bilirubin - direct	34.25	51.53	4.5	0	139
Bilirubin - indirect	35.25	37.74	28.5	0	91
Serum albumin	19.12	16.13	26.5	0	35
aspartate aminotransferase	29.12	37.76	19	0	106
alanine aminotransferase	15.12	16.6	11.5	0	40
gamma-glutamyl transpeptidase	86.38	97.64	79.5	0	285

Table 2: Summary of the number of doses and observations per patient in the preliminary dataset (n=8 individuals)

	N Doses	Observations
Mean	2.625	5.625
SD	1.302	0.744
Median	2	6
Minimum	1	4
Maximum	5	6

After conducting analysis on the NONMEM software, the parameter estimates for the base and final covariate models are detailed in Table . These were a one-compartment (plus depot) model, with first-order elimination, exponential random effects terms to account for IIV, and a proportional error term to account for residual variability. Estimates are given for S-, R-, and S,R-ketamine. It can be seen that ω_{CL} and ω_V both dropped significantly in the Final model (from70% to 48% and from 58% to 27% respectively for the S,R-ketamine data).

Table 3: Parameter estimates for the base and final models in each ketamine dataset (n= 8 individuals)

	S,R-ketamine		S-ketamine		R-ketamine	
Parameter	Base model	Final model	Base model	Final model	Base model	Final model
ΔOBJ	n/a	9.762	n/a	9.712	n/a	9.746
CL (L/hr base, L/hr/70kg final)	4.09	64.9	3.78	59.7	3.93	62.2
V (L or L/70kg)	4.16	169	4.11	167	4.13	168
Ka (hr^{-1})	26.5	25	24.7	23.4	25.6	24.2
ω^2_{CL}	0.499	0.23	0.537	0.27	0.518	0.25
ω_{CL} (%CV)	70.64%	47.96%	73.28%	51.96%	71.97%	50.00%
ω^2_V	0.331	0.0726	0.347	0.0776	0.339	0.0745
ω_V (%CV)	57.53%	26.94%	58.91%	27.86%	58.22%	27.29%
$\omega^2_{K_a}$	0.124	0.153	0.15	0.174	0.137	0.164
ω_{K_a} (%CV)	35.21%	39.12%	38.73%	41.71%	37.01%	40.50%
σ^2_{prop}	0.0265	0.0254	0.0263	0.0251	0.0263	0.0252
σ_{prop} (%CV)	16.28%	15.94%	16.22%	15.84%	16.22%	15.87%

Plots of the measured concentration of each enantiomer of ketamine and norketamine with time revealed consistent trends in all patients in this initial dataset. In each case the concentration of R-ketamine dropped more slowly than that of S-ketamine, while the concentration S-norketamine was consistently higher than that of R-norketamine in all patient plots. Ratios of S:R enantiomer of both ketamine and norketamine over time are given in Figure 2 and Figure . The clear and apparent visual trend for ketamine is for the concentration of S-ketamine to reduce faster than that of R-ketamine, moving from the initial racemate injected towards an enantiomeric excess of R-ketamine. Likewise the apparent visual trend is for norketamine to move from a racemic situation towards a marked enantiomeric excess of S-norketamine.

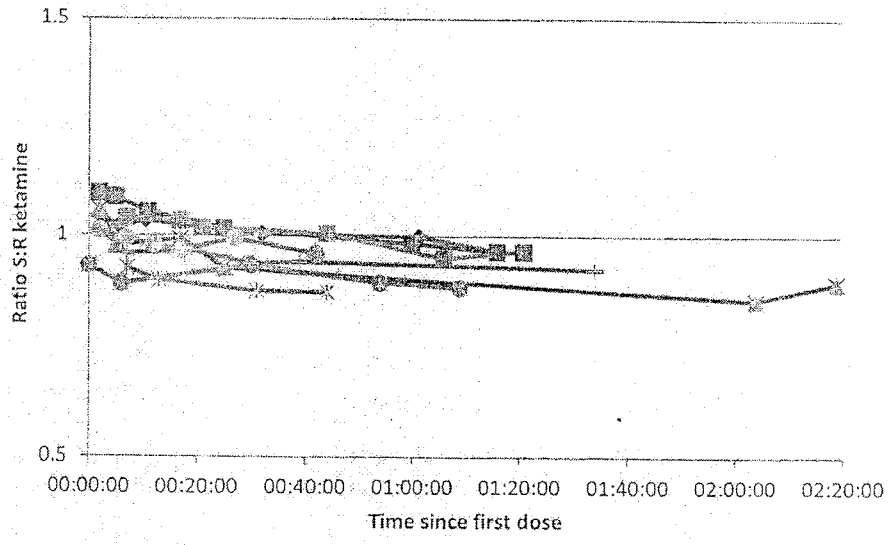

Figure 2: Ratio of S- to R-ketamine over time from first dose in each of the 8 patients

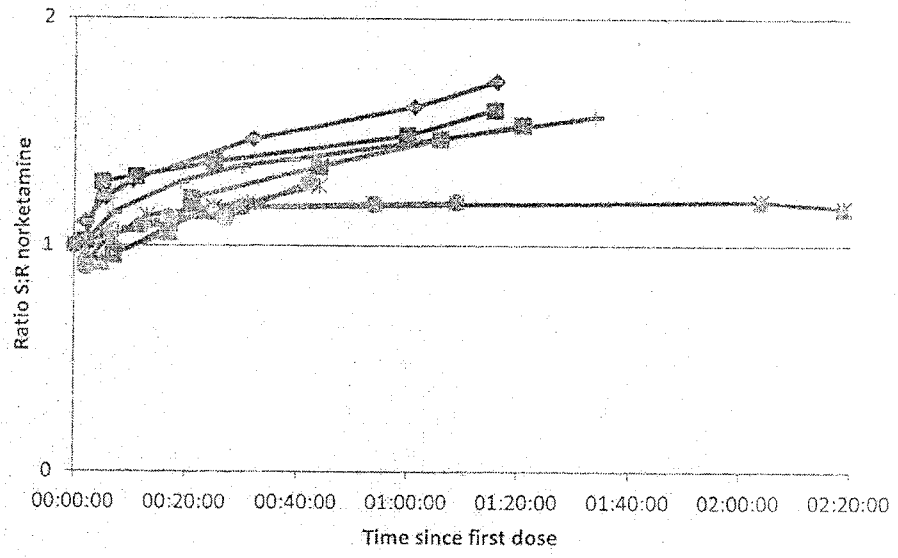

Figure 3: Ratio of S- to R-norketamine over time from first dose in each of the 8 patients

6. Safety Evaluation

- No adverse effects associated with the trial occured.
- No deaths due to trial occurred.

7. Discussion

The final PK model developed in this preliminary study population (n=8 individuals) was based on allometric scaling of S- and R-ketamine clearance by weight, which coincides with studies in older paediatric populations (Herd & Anderson, 2007). There is, however, a suggestion in the visual plots of a trend with Post Natal Age (PNA) on clearance caused by the very young patients in the study – it will be interesting to see if the final dataset at the conclusion of the clinical trial bears that trend out into a significant covariate, or if it is due to sampling in the small patient population analysed thus far. There are two developmental reasons which might provide appropriate hypotheses to explain this trend if it is borne out – firstly it has been reported that maturation of some enzymes is triggered by birth rather than being a continuous development from birth (Alcorn & McNamara, 2002a, Alcorn & McNamara, 2002b), and secondly the clearance of ketamine has been reported to equate to hepatic blood flow (Herd & Anderson, 2007) and it is known that hepatic circulation at birth is very immature, with the end of umbilical blood flow triggering large changes (Montagnani, 1963).

Differences in the metabolism of S-, R- and S,R-ketamine have been reported in the literature. Ihmsen *et al.* (2001) measured the pharmacokinetic parameters of each enantiomer of ketamine in healthy adult volunteers after infusion of S- or S,R-ketamine and found that the presence of R-ketamine in the racemate inhibited in the metabolism of S-ketamine compared to its parameter estimates when infused alone, and that R-ketamine exhibited different parameter estimates to S-ketamine in the racemate. This work added further detail to the earlier observation of a difference between S- and R-ketamine metabolism when the racemate was administered (Geisslinger *et al.*, 1993). These clinical studies have been backed up by *in vitro* experiments with pooled liver microsomes, which again revealed a reduced intrinsic clearance of S-ketamine in the presence of R-ketamine in humans (Schmitz *et al.*, 2010). It has not yet been reported in the literature, however, at what maturational stage these enantiomeric differences manifest themselves.

It is apparent from Figure and Figure that there are differences in the observed concentrations of each enantiomer of ketamine and norketamine. This is in keeping with what is already known about the enantiomeric differences in ketamine

metabolism in adults but reflects the first evidence that these differences exist in the very young. The initial dataset studied (n=8 individuals) here was insufficient for NONMEM to reflect these differences in its estimates, but it is hoped that the final full clinical trial dataset will be sufficient to estimate parameters for each enantiomer and any changes in their metabolism that occur with age. Also of great interest is that a trend towards enantiomeric differences with postnatal age can already be seen in both the η_{CL} vs PNA plots, and in the three post-natally youngest children exhibiting a much lower ratio of S-:R-norketamine than the five post-natally older children, suggesting that the study presented here may be covering the age at which enantiomeric differences become apparent and giving hope that the full study when completed will reveal new and useful information about not just the pharmacokinetics of ketamine in the very young, but also the ontogeny of the relevant hepatic metabolic pathways.

8. Conclusion

The research has shown the usefulness of dried blood spots for obtaining drug level measurements in neonates which allows the study of pharmacokinetics in this vulnerable patient population

A preliminary population pharmacokinetic model for ketamine has been developed in a population of 8 infants, which has suggested that weight is a significant covariate in ketamine clearance. Clearance and volume estimates are comparable with studies in older populations, however, there was an apparent trend towards lower clearance in the post-natally young patients in this study. Two interesting trends were noticed in the visual examination of the data, namely the correlation of clearance with post natal age, and the correlation of the change in enantiomeric ratio with post natal age.

The use of enantioselective analytical methods on the DBS samples has given us the ability to study the maturation of hepatic enzymes systems that are known to exhibit stereoselectivity. The preliminary work presented here on ketamine has shown signs of capturing a developing stereoselective effect within the target patient population, and it is hoped that the final study data will reveal more clearly the maturational patterns in this patient population. Given the well established

enantiomeric differences in pharmacodynamics this information may be clinically important.

The presented DBS-LC-MS/MS-NONMEM methodology opens up the opportunity to study neonatal pharmacokinetics and provide the evidence base required to turn them from *therapeutic orphans* to *therapeutic equals*.

5th July 2013