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)

[P26-4-8] Safety and pharmacokinetics of 2-iminobiotin in neonates with therapeutic hypothermia after perinatal asphyxia

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Keywords: Therapeutic Hypothermia, Pharmacokinetics, Clinical study, Neonatal neuroprotection

Background

Despite treatment with therapeutic hypothermia, 45% of neonates with hypoxic-ischemic encephalopathy (HIE) show an adverse outcome. 2-iminobiotin (2-IB), a selective inhibitor of nNOS and iNOS, has shown neuroprotective properties in animal models, but has not yet been combined with therapeutic hypothermia in humans.

Objective:
In a prospective study safety and pharmacokinetics of 2-IB in addition to therapeutic hypothermia were investigated.

Methods

Term neonates treated with therapeutic hypothermia for HIE were eligible for inclusion. Based on animal data, all infants received four infusions of 0.16 mg/kg 2-IB started within 12h after birth, with 6h intervals. From each patient, five plasma samples were taken at designated time points and area under the concentration time (AUC) curves were calculated and extrapolated to 48h, assuming a total of eight administrations every six hours. Target AUC_{48h} was 4800 ng*h/ml.
Safety was assessed by comparing vital parameters before and after administration of 2-IB to historical matched controls. A significant change of >10% was considered clinically relevant.
2-IB plasma concentrations were analyzed using an LC/MS-MS method. Pharmacokinetic analysis was performed using NONMEM (version 7.3). Statistical analysis was performed using SPSS (version 21.0.0).
This study (NTR5221) was approved by the ethics committee.

Results

Six patients (GA 39.4 wks [range 37.1-41.3]; BW 3490 g [range 2320-4980] were included. One patient died after completing the study protocol after redirection of care. Pharmacokinetic data of 2-IB was best described using a two-compartment model. Median AUC_{48h} was 9544 ng*h/ml. Individual plots show high peak concentrations and little to no accumulation of 2-IB (figure 1). No significant change in heart rate, oxygenation, blood pressure, cerebral saturation, and aEEG was observed after administration of 2-IB compared to historical controls.

Conclusions

The present dosing regimen resulted in higher blood levels than anticipated based on animal models. No

adverse effects that could be attributed to the use of 2-IB were observed.
Six additional patients will be tested with a reduced dose of 0.08 mg 2-IB every six hours; administration will be prolonged to eight infusions.

Figure 1: PK plots of 2-IB for each individual patient

Zoom image