
Poster

[P26-2] P26-2: Central nervous system drugs (1)

Chair: Atsushi Yonezawa, Japan

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[P26-2-1] Phenobarbital pharmacokinetics during therapeutic hypothermia after perinatal asphyxia: evaluation of an existing model

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Background

Pharmacokinetics of drugs may be affected by therapeutic hypothermia in full term neonates with perinatal asphyxia. Little information is available on the pharmacokinetics of drugs frequently administered during therapeutic hypothermia and evidence based dosing guidelines are needed.

Objective:

In the prospective, nationwide PharmaCool study (NTR2529) pharmacokinetics of phenobarbital, a first line anti-epileptic drug, were studied. Aim of this study was to evaluate a pharmacokinetic model of phenobarbital under therapeutic hypothermia as published previously (*Clin Pharmacokinet* 2012 51:671-679).

Methods

Term neonates who received phenobarbital while treated with therapeutic hypothermia following perinatal asphyxia were eligible. Phenobarbital was administered as a single or repeated injections. A maximum of four plasma samples were obtained during the first 120 hours after birth during both hypothermia and normothermia. Phenobarbital plasma concentrations were analyzed using a validated LC-MS/MS method. Pharmacokinetic analyses were performed using NONMEM (version 7.3).

Results

For 113 patients (GA 39.8 wks [range 36.0-42.0]; BW 3384 g [range 2090-5000] phenobarbital dosing information and at least one plasma level were available. Plasma levels ranged from 3.10 to 52.6 mg/L (figure 1). In 49 patients only a loading dose was given, 64 patients required additional phenobarbital dosing. In 22% of the patients, phenobarbital was followed by a second anti-epileptic drug. Population parameters scaled to 3.5 kg were 10.40 ml/h for clearance and 3,610 ml for volume of distribution. No significant effect of therapeutic hypothermia on clearance of phenobarbital could be identified.

Conclusions

We confirmed that therapeutic hypothermia has no influence on phenobarbital pharmacokinetics in this patient population. Dosing adjustment of phenobarbital during therapeutic hypothermia is not necessary. Plasma levels after a single phenobarbital injection are often low; clinicians should not be reluctant to administer an additional phenobarbital dose if required.

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Figure 1: observed phenobarbital plasma concentrations (single dose only). Dotted lines indicate the therapeutic window (10-40 mg/L)

[Zoom image](#)