CSF and Plasma Pharmacokinetics of Flurbiprofen in Children

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Objectives

Recently, there has been discussion about possible central effects of NSAIDS. The aim of this study was to investigate the distribution of flurbiprofen into cerebrospinal fluid (CSF) in children. The CSF and plasma pharmacokinetics of flurbiprofen in children (aged between 3 months and 13 years, n=64) were examined and the absolute bioavailability of oral flurbiprofen suryp was estimated. Previously, there had been only one study of flurbiprofen pharmacokinetics in children [1].

Methods

The study included 64 children, aged between 3 months and 13 years. An intravenous dose (circa 0.65 mg/kg) of flurbiprofen axetil was given to 27 patients and an oral dose (1 mg/kg) of flurbiprofen syrup was given to 37 patients.

A total of 304 blood samples (1-7 samples per patient) and 64 CSF samples were obtained. From these, 304 total plasma, 62 unbound plasma and 60 CSF concentrations were measured by gas chromatography with mass spectrometric detection. Modeling was done with NONMEM VI 2.0.

- The data were best described by a three-compartment model (dOFV between 2-comp and 3-comp: 25).
- The concentrations in CSF were about sevenfold higher than those in unbound form in plasma. Hence, an uptake factor (UPTK) was implemented along with intercompartmental clearance QCSF to describe the accumulation of flurbiprofen into CSF. The rate "central to CSF" was scaled by f_u. Accordingly:

  $K25=QCSF*f_u*UPTK/V2$

  $K52=QCSF/V5$

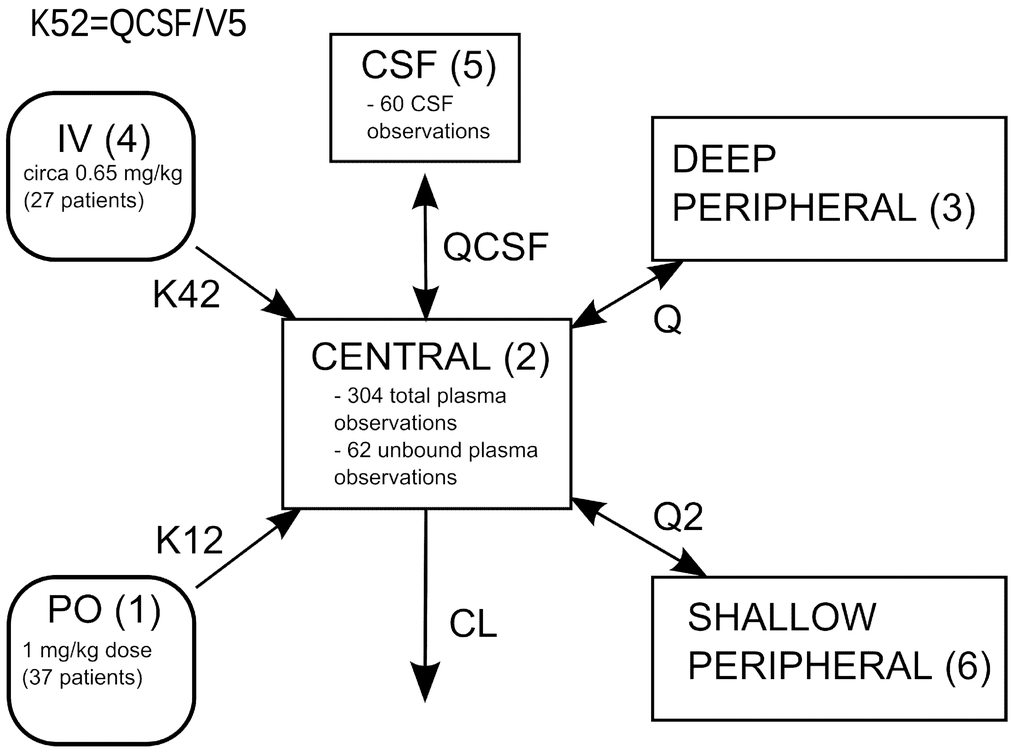

Figure 1: A diagram of the model

Results

Summary:

- The bioavailability of flurbiprofen in children is 0.8
- The uptake factor was estimated to be 6.8
- Age did not significantly affect clearance after allometric scaling by weight had been included as a covariate.
- The residual error in CSF observations is high (σ_{CSF}=0.50).
- The concentrations of flurbiprofen in CSF were higher (circa sevenfold) than unbound flurbiprofen concentrations in plasma.

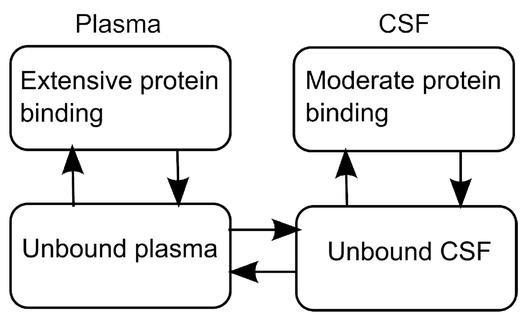

Figure 2: Protein binding in CSF could explain the CSF concentrations being higher than unbound plasma concentrations.

Table 1: The parameter estimates of the final model

Parameter, unit	Estimate	Relative Standard Error (NONMEM)	Relative Standard Error (Bootstrap)
Bioavailability	0.81	0.055	0.061
Oral absorption rate constant, 1/h	5.5	0.24	0.42
Lagtime, oral absorption, h	0.11	0.16	0.43
IV absorption rate constant, 1/h	29	0.32	0.64
Clearance, L/h * (WT/70)^0.75	0.96	0.057	0.071
V(central), L * (WT/70)	3.6	0.11	0.13
Q(shallow peripheral), L/h	1.5	0.39	0.51
V(shallow peripheral), L * (WT/70)	1.8	0.20	0.20
Q(deep peripheral), L/h	0.18	0.30	0.34
V(deep peripheral), L * (WT/70)	2.7	0.18	0.26
Fraction unbound	0.00031	0.043	0.038
QCSF, L/h	0.12	0.27	0.31
Uptake to CSF	6.8	0.070	0.063
ω_{CL}	0.28	0.20	0.21
ω_{fu}	0.30	0.28	0.29
ω_{Vd}	0.28	0.25	0.27
ω_{K12}	0.81	0.40	0.59
$\sigma_{blood\ plasma}$	0.13	0.065	0.069
σ_{CSF}	0.50	0.091	0.086

Conclusions

This is the first study to address the CSF distribution of flurbiprofen in humans. This study is also first to address the pharmacokinetics of flurbiprofen in children younger than 6 years old and to estimate the absolute bioavailability of flurbiprofen in children.
Total flurbiprofen concentrations in CSF are higher than unbound flurbiprofen concentrations in plasma, which is typical to lipophilic drugs with extensive protein binding[2]. However, we cannot exclude the possibility of active uptake.

References

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[2] Shen D, Artru A, Adkison K. Principles and applicability of CSF sampling for the assessment of CNS drug delivery and pharmacodynamics. Adv Drug Deliv Rev, 2004. 56(12): p. 1825-57.

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