Plasma and cerebrospinal fluid pharmacokinetics of flurbiprofen in children

Elina Kumpulainen,^{1,2*} Pyry Väitalo,^{3*} Merja Kokki,²
Marko Lehtonen,⁴ Andrew Hooker,⁵ Veli-Pekka Ranta³ &
Hannu Kokki²

¹Department of Pharmacology and Toxicology, University of Eastern Finland, Kuopio, ²Department of Anaesthesiology and Intensive Care, Kuopio University Hospital, Kuopio, ³Department of Pharmaceutics, University of Eastern Finland, Kuopio, ⁴Department of Pharmaceutical Chemistry, University of Eastern Finland, Kuopio, Finland and ⁵Department of Pharmaceutical Biosciences, University of Uppsala, Uppsala, Sweden

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

Flurbiprofen is a commonly used non-steroidal anti-inflammatory drug in children to treat pain and fever. There is limited information on the pharmacokinetics of flurbiprofen in children and no data on the cerebrospinal fluid permeation of flurbiprofen.

WHAT THIS STUDY ADDS

Our population pharmacokinetic model indicates that weight-based dosing of flurbiprofen is appropriate in children older than 6 months. The bioavailability of oral flurbiprofen syrup is high, 71–91%, and thus, the oral syrup provides accurate dosing in paediatric patients. Cerebrospinal fluid concentrations of flurbiprofen are markedly higher than the unbound plasma concentrations.

Correspondence

Dr Hannu Kokki, Department of Anaesthesiology and Intensive Care, Kuopio University Hospital, PO Box 1777, FI-70211 Kuopio, Finland.
Tel.: + 358 44 717 4654
Fax: + 358 17 17 3443
E-mail: hannu.kokki@kuh.fi

*Equal contribution.

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AIMS

This study was designed to characterize paediatric pharmacokinetics and central nervous system exposure of flurbiprofen.

METHODS

The pharmacokinetics of flurbiprofen were studied in 64 healthy children aged 3 months to 13 years, undergoing surgery with spinal anaesthesia. Children were administered preoperatively a single dose of flurbiprofen intravenously as prodrug ($n = 27$) or by mouth as syrup ($n = 37$). A single cerebrospinal fluid (CSF) sample ($n = 60$) was collected at the induction of anaesthesia, and plasma samples ($n = 304$) before, during and after the operation (up to 20 h after administration). A population pharmacokinetic model was built using the NONMEM software package.

RESULTS

Flurbiprofen concentrations in plasma were well described by a three compartment model. The apparent bioavailability of oral flurbiprofen syrup was 81%. The estimated clearance (CL) was $0.96 \text{ l h}^{-1} 70 \text{ kg}^{-1}$. Age did not affect the clearance after weight had been included as a covariate. The estimated volume of distribution at steady state (V_{ss}) was $8.1 \text{ l } 70 \text{ kg}^{-1}$. Flurbiprofen permeated into the CSF, reaching concentrations that were seven-fold higher compared with unbound plasma concentrations.

CONCLUSIONS

Flurbiprofen pharmacokinetics can be described using only weight as a covariate in children above 6 months, while more research is needed in neonates and in younger infants.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used analgesics and antipyretics in paediatric pharmacotherapy [1, 2]. Flurbiprofen is probably one of the most commonly used NSAIDs in many countries. However, the paediatric pharmacokinetics (PK) of flurbiprofen are poorly known. To the best of our knowledge, the PK of oral and rectal flurbiprofen have only been studied in eight children aged 6–12 years [3].

An intravenous (i.v.) formulation of flurbiprofen was developed in Japan in 1996 [4]. This formulation contains a prodrug, flurbiprofen axetil, since plain flurbiprofen as an injection causes venous irritation [4]. Flurbiprofen axetil is hydrolyzed into flurbiprofen by blood esterase in a few minutes [4, 5]. We are unaware of any paediatric PK studies of i.v. flurbiprofen axetil. However, this information is important because i.v. administration is the most accurate route in acute pharmacotherapy such as postoperative pain management [2]. In addition, data on the rate and extent of central nervous system (CNS) permeation of flurbiprofen would be interesting because the antihyperalgesic and antipyretic activities of flurbiprofen and other NSAIDs have been proposed to be partly mediated by spinal and CNS mechanisms [6, 7].

In the present study we have evaluated and validated a model for the PK of oral and i.v. flurbiprofen and investigated the CSF permeation of flurbiprofen in children aged between 3 months and 13 years. Population PK modelling was used to identify the most significant patient characteristics that can be used to describe and predict flurbiprofen PK in this patient group. Analgesic concentrations of flurbiprofen were observed in patients undergoing inguinal surgery.

Methods

Ethical considerations

The study was approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (no. 12/2006), and it was conducted in accordance with the principles of the Declaration of Helsinki. The Finnish National Agency for Medicines was notified (no. 6/2006) and the protocol was recorded in the EudraCT database (no. 2006-000310-20). The parents and children old enough to understand the implications of taking part in the study were given oral and written information on the trial protocol. The parents provided a written consent and the children old enough an assent.

Patients

Parents of 80 children were asked to participate in the study and 65 parents gave consent. A total of 64 healthy children, scheduled for elective surgery in the lower part of

the body with spinal anaesthesia, were included in the study. One child was excluded because his operation was postponed. All surgery was of a minor nature, with relatively low or no blood loss.

Treatments

In a parallel group study, the patients were given a single preoperative dose of flurbiprofen by mouth or i.v.. Thirty-seven patients were administered 1 mg kg⁻¹ of flurbiprofen syrup (Froben, 5 mg ml⁻¹, Abbott, Campoverde, Italy), and 27 patients a 10 min i.v. injection of 0.9 mg kg⁻¹ of flurbiprofen axetil (Ropion 10 mg ml⁻¹, Kaken Pharmaceutical, Tokyo, Japan), a prodrug of flurbiprofen, which corresponds about 0.65 mg kg⁻¹ of flurbiprofen. Premedication, spinal anaesthesia and sedation were standardized. Transmucosal midazolam and ketamine were given as premedication, propofol and thiopental i.v. were used for intraoperative sedation, paracetamol and ketoprofen were given for postoperative pain and fentanyl for rescue analgesia.

Sampling and analytical methods

A total of 304 blood samples were obtained during the perioperative period. The sampling was done between 5 min and 20 h after flurbiprofen administration. The number of blood samples taken from an individual patient ranged between one and seven. Of these, 304 total flurbiprofen plasma concentrations and 63 protein-free flurbiprofen plasma concentrations were analyzed. One protein-free flurbiprofen measurement was excluded from the data because of being an outlier.

All 64 patients had a CSF sample taken during the lumbar puncture for spinal anaesthesia before the injection of local anaesthetic. The CSF was obtained between 15 min and 18 h after flurbiprofen administration. In one CSF sample the flurbiprofen concentration was below the limit of quantification and was not included in the PK analysis. Furthermore, nine of the CSF samples were stained reddish, which implied that blood had contaminated the sample. In three of these stained CSF samples the ratio of flurbiprofen concentration in CSF vs. protein-free flurbiprofen in plasma was significantly higher than in other samples. These samples were not included in the dataset. Furthermore, the remaining six samples were marked with a special flag in the dataset and the staining was tested as a covariate to see if it had any effect on the model. The result was that staining made no difference and the six samples were included in the PK model. Thus, a total of 304 total flurbiprofen plasma concentrations, 62 protein-free flurbiprofen plasma concentrations and 60 total flurbiprofen CSF concentrations were included in the data set.

The method of analysis was gas chromatography with mass spectrometric detection. Flurbiprofen was isolated from CSF (500 µl), plasma (100 µl) and protein free plasma (100 µl) by solid phase extraction. Ion monitoring

at 243 m/z was used for pentafluorobenzyl derivative of flurbiprofen detection. The calibration range of the method was 0.4–80, 125–20 000 and 0.1–30 ng ml⁻¹ for CSF, plasma and protein-free plasma samples, respectively. Free flurbiprofen was extracted from plasma by ultrafiltration using Centrifree® Micropartition Devices (Millipore Corp., Bedford, MA, USA). The method is explained in detail in our previous paper [8].

Determination of analgesic flurbiprofen concentrations

Additional blood samples were collected from children undergoing inguinal surgery at the onset of first wound pain after surgery and spinal anaesthesia. The onset of pain was assessed both by observation at every 15 min and children's own expression.

Modelling strategy and population pharmacokinetic model

Data were analyzed using the NONMEM software package (version VI, level 2.0; ICON Development Solutions, Ellicott City, MD, USA) with the DIGITAL FORTRAN compiler. The first-order conditional estimation method with interaction was used.

A three compartment model with first-order absorption for both oral dosing and i.v. prodrug dosing, and first-order elimination was used to describe the data (Figure 1). The conversion of flurbiprofen axetil into flurbiprofen was described using a first order rate constant from a prodrug dosing compartment into the central compartment. An absorption compartment with lag time was used to describe oral absorption.

Unbound observations were included in the same compartment as total plasma observations. They were defined as special cases of total plasma observations,

Figure 1

Structural model for flurbiprofen. Symbols: K12, oral absorption rate constant; K42, absorption rate constant for flurbiprofen from i.v. prodrug dosing compartment; CL, clearance; Q2, intercompartmental clearance between central and shallow peripheral compartment; Q, intercompartmental clearance between central and deep peripheral compartment; QCSF, intercompartmental clearance between central and cerebrospinal fluid (CSF) compartment; UPTK, uptake multiplier for the transfer of unbound flurbiprofen from central to CSF compartment

which have to be multiplied by f_u . The distribution of flurbiprofen into CSF was described with an intercompartmental clearance QCSF together with UPTK. The transfer rate from central compartment to CSF was scaled by fraction unbound and UPTK. Thus:

$$K_{\text{central to CSF}} = \text{QCSF} \times f_u \times \text{UPTK} / V_{\text{central}}$$

$$K_{\text{CSF to central}} = \text{QCSF} / V_{\text{CSF}}$$

where $K_{\text{central to CSF}}$ is the rate constant for drug transfer from central compartment to CSF and $K_{\text{CSF to central}}$ is the rate constant for drug transfer from CSF to central compartment. QCSF is the intercompartmental clearance between CSF and central compartment and UPTK is the uptake factor which multiplies the rate from central compartment to CSF compartment. f_u is the fraction unbound. V_{CSF} and V_{central} are the volumes of CSF compartment and central compartment, respectively.

Between-subject variability (BSV) was tested for all fixed parameters with a criteria corresponding to approximately $P < 0.01$. BSV was assigned to volume of distribution, clearance, oral absorption rate and fraction unbound with an exponential model, e.g.

$$\text{PARM} = \theta_{\text{TV}} \times e^{\eta}$$

where θ_{TV} is the typical value of the parameter and η is a random parameter (random-effect) different for each individual derived from a normal distribution with mean zero and variance ω^2 . Between-subject variability was best described as uncorrelated. Covariance between random effects was explored, but none was found to be significant.

For residual error, a proportional error model with separate variances for plasma and CSF observations proved adequate. Additive, proportional and slope-intercept error models were tested separately for each type of observation (total flurbiprofen in plasma, unbound flurbiprofen in plasma and total flurbiprofen in CSF).

Covariates that were included in the analysis were gender, fasting (0 if fasting had lasted less than 3 h, 1 if fasting had lasted 3 h or longer), treatment, weight, height and age. Covariate relationships were explored using the GAM function of the Xpose 4.0 software (<http://xpose.sf.net> [9]), and by regularly checking plots of random effects vs. covariates. Also, if literature suggested a remarkable relationship between a covariate and a parameter, the relationship was investigated. For a covariate to be included, it was required to have a physiological rationale and to have a significance of approximately $P < 0.01$.

Categorical covariates (where CA = 0 or CA = 1) were tested in the following manner:

$$\text{PARM} = \theta_{\text{TV}} \times (1 + \text{CA} \times \theta_2)$$

Continuous covariates were tested with various models including slope + intercept model, allometric scaling and non-exponential scaling. The allometric equation for

clearance was the following: A typical value of clearance for 70 kg person is estimated with an exponent for scaling into different bodyweights.

$$CL = \theta_{CL} \left(\frac{WT}{70} \right)^{\theta_{\text{exponent}}}$$

where CL is clearance, WT is bodyweight and θ_{CL} is the estimated parameter that signifies clearance for a typical individual weighing 70 kg. θ_{exponent} is the estimated parameter for the exponent used in scaling by weight.

For clearance, an allometric exponent of 0.775 was estimated. This is in close agreement with the value 0.75 reported in literature [10], and thus the exponent was set to 0.75. For volume of distribution, likewise, an exponent of 1.01 was estimated, which is in close agreement with value of 1 suggested in the same literature [10]. Thus, the exponent for volume of distribution was set to 1.

The shrinkages of both Empirical Bayes Estimates (η -shrinkage) and residual errors (ε -shrinkage) were calculated. The equations for calculation of η -shrinkage and ε -shrinkage were as follows:

$$\eta\text{-shrinkage} = 1 - \frac{SD(EBEs)}{\omega}$$

$$\varepsilon\text{-shrinkage} = 1 - SD(IWRES)$$

Model evaluation

The model was evaluated by performing a bootstrap, a visual predictive check (VPC) and a numerical predictive check (NPC).

The bootstrap involved mixing the original dataset into 200 new datasets. The parameters were then re-estimated for these new datasets according to the specifications of the final model. The (parametric) relative standard errors of parameter estimates were calculated and (non-parametric) 95% confidence intervals for parameter estimates were obtained. The purpose of the bootstrap was to check the robustness of the model and to provide an alternative way to estimate uncertainty of parameter values [11].

Table 1

Patients' baseline characteristics ($n = 64$). Data are number of cases and median (range)

Variable	Both groups $n = 64$	Oral group $n = 37$	Intravenous group $n = 27$
Gender (girls/boys)	15/49	9/28	6/21
Age (years)	5.2 (0.25–13)	4.7 (0.25–13)	5.6 (0.25–13)
Weight (kg)	20 (7–76)	19 (7–76)	20 (8–55)
Height (cm)	110 (60–167)	110 (63–167)	115 (60–146)
Operations, n			
Herniotomy	26	14	12
Orthopaedic surgery	13	9	4
Genitourinary surgery	12	6	6
Other	13	8	5

The VPC involved the generation of 500 simulated flurbiprofen concentration sets from the final population model parameters using the NONMEM software package. The 2.5th, 50th, and 97.5th percentiles of the simulated concentrations at each time point were overlaid in lines and shown together with observed data for visual inspection. The VPC was grouped into four different graphs: total flurbiprofen in both oral and i.v. treatment groups, unbound flurbiprofen in both groups and CSF flurbiprofen concentrations in both groups.

The NPC involved the generation of 500 simulated flurbiprofen concentration sets according to the final model. For each data point the prediction interval from the simulations were compared with the observation. The percentage of observations lying outside of their prediction intervals was then calculated and compared with the expected number. Confidence intervals for the expected number of observations lying outside their prediction interval were also computed [12]. The NPC grouping was done in the same manner as for the VPC.

Results

Demographic data

There were no differences between the oral and i.v. dosing groups (Table 1). The number of children and plasma samples in each age group are shown in Figure 2. All patients received the study drug according to the protocol, and no protocol deviations likely to affect the results were observed.

Observed concentrations

A total of 304 flurbiprofen plasma concentrations, 62 protein-free flurbiprofen plasma concentrations and 60 total flurbiprofen CSF concentrations were used in the modelling (Figure 3). The flurbiprofen concentrations during the first 30 min after i.v. dosing ranged from 5.4 to 14 (median 9.6) mg l⁻¹. The highest concentrations after oral dosing were observed within 1 h post-dose.

Figure 2

The number of patients and samples in different age groups: (A) The number of patients in different age groups (total $n = 64$) and (B) the number of plasma samples taken from each age group (total $n = 304$)

Figure 3

Flurbiprofen concentrations: (A) i.v. group ($n = 27$), total plasma concentrations, (B) oral group ($n = 37$), total plasma concentrations, (C) both groups, protein-free plasma concentrations and (D) both groups, total CSF concentrations

The flurbiprofen concentrations at 30–60 min post-dose varied between 4.5 and 15 (median 8.7) mg l⁻¹. The CSF concentrations of flurbiprofen ranged between 0.4 and 36.2 µg l⁻¹. Flurbiprofen was detected both in the earliest CSF sample obtained at 15 min after i.v. dosing (8 µg l⁻¹) and in the earliest CSF sample after oral dosing (0.4 µg l⁻¹), and the highest CSF concentrations were observed about 1–2 h post-dose with both administration routes. In one patient, the CSF concentration of

flurbiprofen at 20 min after oral dosing was below the limit of quantification.

Population pharmacokinetic model

The parameter estimates, their (parametric) standard errors and nonparametric confidence intervals were estimated directly by the NONMEM software package and by a bootstrap procedure (Table 2).

Table 2

Pharmacokinetic parameter estimates and relative standard errors of the final model. Relative standard errors were calculated by dividing the standard error of a parameter by the estimate of the parameter

Parameter (units)	Estimate	Relative standard error (NONMEM)	Confidence range 2.5th–97.5th percentile (Bootstrap)
Bioavailability	0.81	0.055	0.71–0.91
Oral absorption rate constant (K_{12}) (l h^{-1})	5.5	0.24	2.9–15
Lag time, oral absorption (h)	0.11	0.16	0.045–0.27
i.v. absorption rate constant (K_{42}) (l h^{-1})	29	0.32	16–94
$\text{CL } (\text{l h}^{-1}) \times (\text{WT}/70)^{0.75}$	0.96	0.057	0.83–1.1
$V \text{ (central) } (\text{l}) \times (\text{WT}/70)$	3.6	0.11	2.6–4.5
$Q \text{ (shallow peripheral) } (Q_2) (\text{l h}^{-1})$	1.5	0.39	0.58–4.4
$V \text{ (shallow peripheral) } (\text{l}) \times (\text{WT}/70)$	1.8	0.20	1.0–2.6
$Q \text{ (deep peripheral) } (\text{l h}^{-1})$	0.18	0.30	0.097–0.32
$V \text{ (deep peripheral) } (\text{l}) \times (\text{WT}/70)$	2.7	0.18	2.0–4.8
Protein-free fraction	0.00031	0.043	0.00029–0.00034
$Q_{\text{CSF}} (\text{l h}^{-1})$	0.12	0.27	0.073–0.23
Uptake to CSF (UPTK)	6.8	0.070	6.0–7.7
ω_{CL}	0.28	0.20	0.22–0.34
ω_{fu}	0.30	0.28	0.19–0.36
ω_{vd}	0.28	0.25	0.19–0.35
$\omega_{K_{12}}$	0.81	0.40	0.42–1.4
$\sigma_{\text{blood plasma}}$	0.13	0.065	0.11–0.14
σ_{CSF}	0.50	0.091	0.43–0.60

Weight was identified as a significant covariate for both flurbiprofen clearance and volume of distribution. Allometric scaling with an exponent of 0.75 for clearance and 1 for volume of distribution was used when implementing weight as a covariate [10]. Age did not affect the clearance of flurbiprofen after allometric scaling by weight had been taken into account. Furthermore, there did not seem to be differences in the magnitude of the variability of clearance in the youngest patients. Height, gender and duration of fasting were not significant covariates in this study.

The plasma concentrations were best described with a three compartment model, and a separate compartment was used for CSF observations (Figure 1, Table 2). When scaled to a 70 kg person, the volumes describing plasma kinetics were 3.6 l for the central compartment, 2.7 l for the deep peripheral compartment and 1.8 l for the shallow peripheral compartment. The volume of the CSF compartment (0.15 l) was retrieved from the literature [13] and also scaled by weight. The clearance of flurbiprofen was 0.96 l h^{-1} when scaled to a 70 kg person.

The oral absorption rate constant (K_{12}) of flurbiprofen was 5.5 h^{-1} and the lag time for oral absorption was 6 min. The apparent bioavailability of oral flurbiprofen syrup was 81%. When a plasma concentration curve was simulated for a typical patient weighing 20 kg with an oral dose of 1 mg kg^{-1} , the predicted t_{max} was 27 min and C_{max} 10 mg l^{-1} .

After i.v. injection of flurbiprofen axetil, two early plasma samples were taken from five patients. In these

patients, a delay was observed in the peak concentration of flurbiprofen. This is probably due to the conversion of flurbiprofen axetil into flurbiprofen. For this reason, an absorption rate constant (K_{42}) was used for the transfer of flurbiprofen from the i.v. prodrug dosing compartment into the central compartment and its value was estimated to be 29 h^{-1} (half-life of 1.4 min).

Flurbiprofen permeated into the CSF. When comparing the CSF and protein-free plasma concentrations, which were taken within 5 min of each other, the CSF concentrations were about seven times higher than protein-free plasma concentrations. The fraction unbound in plasma was found to be constant in the observed concentration range (0.68 to 13.4 mg l^{-1}) with a protein-free fraction of 0.031%. An uptake multiplier (UPTK) was implemented to describe the higher concentrations of flurbiprofen in CSF than in protein-free plasma. UPTK was estimated to be 6.8, which is in agreement with the raw data. The model-predicted C_{max} and t_{max} for CSF concentrations after i.v. injection (0.65 mg kg^{-1}) in a typical 20 kg child were $14 \mu\text{g l}^{-1}$ and 40 min, respectively. The model-predicted CSF C_{max} and t_{max} after oral dosing (1 mg kg^{-1}) were $17 \mu\text{g l}^{-1}$ and 60 min, respectively.

The inter-individual variability was estimated to be roughly 30% for clearance, volume of distribution and fraction unbound (see Table 2). The inter-individual variability for the oral absorption rate constant was estimated at 80%. The shrinkage for Empirical Bayes Estimates (EBEs) and residual errors were as follows: shrinkage(η_{CL}) = 0.077, shrinkage(η_v) = 0.12, shrinkage(η_{fu}) = 0.10, shrinkage(η_{KA}) = 0.45 and shrinkage(IWRES) = 0.21.

Model evaluation

Uncertainty in parameter estimates was low (Table 2). The bootstrap gave (parametric) standard errors that were, in general, slightly higher than those given by the NONMEM software package indicating non-normal distributions of the standard errors as also indicated by the non-parametric 95% confidence intervals.

The VPC results are given in Figure 4. In the VPC, the percentile intervals describing observed concentrations should mostly reside inside the 95% confidence intervals for the percentile intervals describing the simulated concentrations. Overall, the model describes total plasma concentrations well (Figure 4, panels A and B). There is more variability in protein-free plasma concentrations because of the estimated inter-individual variability in plasma protein binding (panel C). Finally, CSF concentrations have wide prediction intervals (panel D) because of the wide variability in the data.

The NPC results indicate good model agreement to data with a slight over-prediction of protein-free plasma concentration at the lower limit of the 80th percentile prediction interval (Figure 5).

Analgesic flurbiprofen concentrations

After inguinal surgery, analgesic flurbiprofen concentrations were measured from 14 patients after i.v. dosing and 11 patients after oral dosing. The median (range) concentration of flurbiprofen at the time of pain occurrence was 3.7 (0.9–6.8) mg l⁻¹ in the i.v. dosing group and 2.9 (0.9–6.9) mg l⁻¹ in oral dosing group (Figure 6).

Adverse effects

Nine adverse effects occurred in nine children. After i.v. dosing, pain in the injection site ($n = 1$), vomiting ($n = 1$), agitation ($n = 1$) and nightmares ($n = 1$) were observed. After oral dosing, nausea ($n = 2$), vomiting ($n = 2$) and agitation ($n = 1$) were observed.

Discussion

We have constructed and validated a model for describing the PK of flurbiprofen in children aged 3 months to 13 years. The model can be used to improve clinical practice and to design future clinical trials. During modelling,

Figure 4

Results of the visual predictive check: (A) i.v. group ($n = 27$), total plasma concentrations, (B) oral group ($n = 37$), total plasma concentrations, (C) both groups, protein-free plasma concentrations and (D) both groups, total CSF concentrations. The black line on the centre represents median observed concentrations and the dotted black lines 2.5th and 97.5th percentile intervals for observations. The grey areas represent 95% confidence intervals for 2.5th, 50th and 97.5th percentile prediction intervals

Figure 5

Results of the numerical predictive check: (A) i.v. group ($n = 27$), total plasma concentrations, (B) oral group ($n = 37$), total plasma concentrations, (C) both groups, protein-free plasma concentrations and (D) both groups, total CSF concentrations. The connected black dots represent the ratio of the number of observations that are outside their own prediction intervals to the expected number (e.g. 5% of data are expected to be outside a 95% prediction interval, 2.5% above and 2.5% below). The dotted lines represent the 95% confidence intervals for this ratio given the correct model. The observations are similar to model-simulated values if the ratio Observed/Expected stays close to 1, and inside the confidence interval

Figure 6

The time and concentration of flurbiprofen when pain occurred after inguinal surgery ($n = 25$). The filled circle represent the oral dosing group and the open circles represent the i.v. group. i.v. dosing (○); oral dosing (●)

weight was identified as the most important covariate for clearance and volume of distribution. The analgesic flurbiprofen concentrations were not included in the population PK model because there were only 25 observations of analgesic concentrations, and the pain occurrence was highly variable in children after inguinal surgery and spinal anaesthesia.

The rapid absorption of oral flurbiprofen syrup makes it an attractive alternative to i.v. dosing for those patients who are able to swallow the drug. The concentrations achieved through oral syrup dosing were quite consistent and thus oral dosing appears to be a reliable method of administering flurbiprofen.

During the model development (see section Methods: modelling strategy), the exponents for the scaling of volume of distribution and clearance were estimated. These estimated values (SE) were 1.01 (0.069) and 0.774 (0.06), respectively. This is in agreement with the allometric scaling theory, in which fixed values of 1 and 0.75 are used [10]. For this reason, the exponents were fixed to 1 and 0.75 in this study.

The main route for flurbiprofen clearance involves metabolism by CYP2C9 [14]. The CYP2C9 expression is

impaired and more variable in children younger than 5 months [15]. No impairment of clearance was apparent for children aged less than 5 months (three patients) or children aged less than 2 years (14 patients). Furthermore, no heightened variability in clearance was found in either of these groups. However, it is possible that our population included too few patients aged less than 5 months to reveal the difference in clearance (three children with 13 observations). Earlier, ibuprofen clearance has been shown to increase dramatically during the first postnatal days [16]. Since ibuprofen is also eliminated primarily through CYP2C9 [17], it is possible that flurbiprofen clearance is impaired in neonates.

Our results agree with those of the earlier flurbiprofen study in eight children aged 6–12 years [3] in which a mean V_d/F of 0.15 l kg⁻¹ for oral syrup was estimated. This is very close to our estimate of 0.14 l kg⁻¹ at steady state, when bioavailability (F) is taken into account. On the other hand, our estimate of apparent clearance (CL/F) partly disagrees with that in the previous study. The previous flurbiprofen study was divided into two groups by weight. For the first group (mean weight 18.6 kg), the average CL/F was 0.48 l h⁻¹, which agrees with our result of 0.44 l h⁻¹. For the second group (mean weight 33.9 kg), the mean CL/F was 1.11 l h⁻¹, which is higher than our estimate of 0.68 l h⁻¹. The disparity likely results from two relatively high individual CL/F values observed in the previous study [3].

Our results on the PK of flurbiprofen in children are consistent with those for adults. Our estimated V_d/F (10 l at steady state for a 70 kg person) is in agreement with the previously reported values in range of 9.1–12.4 l [5, 18–20]. Our CL/F estimate of 1.2 l h⁻¹ for a 70 kg person agrees with the reported value of 1.2 l h⁻¹ for adults [5, 19, 20]. The bioavailability of oral flurbiprofen in adults is approximately 90% based on the AUC values reported by Tohno *et al.* [5]. This is in agreement with our estimate of 81% (95% confidence interval of 71, 91%) in children.

Our estimate of fraction unbound of 0.031% for flurbiprofen is similar to the reported values of 0.022–0.11% at therapeutic concentration ranges [18, 21, 22]. Flurbiprofen is in general one of the most highly protein-bound NSAIDs [22, 23].

The accumulation of flurbiprofen into the CSF, with concentrations that are sevenfold compared with protein-free plasma concentrations, is to our knowledge greater than with any other NSAID. Diclofenac, ibuprofen and indomethacin have been reported to reach CSF concentrations that are two- to five-fold compared with unbound plasma concentrations [8, 24–26]. Ketorolac, on the other hand, reaches CSF concentrations that are less than unbound plasma concentrations [27]. Ketoprofen seems to reach CSF concentrations that are similar to unbound plasma concentrations within 1 h of i.v. administration [28, 29].

One likely explanation for this accumulation of drugs into the CSF is that there is protein binding in the CSF,

which has indeed been documented for indomethacin [30]. The concentration of proteins in CSF is about 0.5% of that in plasma [31, 32]. It seems likely that the accumulation of flurbiprofen into the CSF is, to some extent, a result of high lipophilicity and protein binding. However, the possibility of active uptake cannot be ruled out.

We determined the analgesic plasma concentrations of flurbiprofen in 25 children undergoing inguinal surgery with spinal anaesthesia. The analgesic concentrations of flurbiprofen and the time of pain occurrence were variable, and thus, these results should be considered as preliminary. The median plasma concentration of flurbiprofen at the time of pain occurrence was 3–4 mg l⁻¹ after oral and i.v. dosing. Earlier, intravenous flurbiprofen (1 mg kg⁻¹ as axetil prodrug) was used to reduce postoperative pain in children aged 2–12 years after ophthalmologic surgery [33, 34], but the plasma concentrations of flurbiprofen were not determined in these studies.

In conclusion, our data suggest that weight alone is a feasible covariate for predicting the PK of flurbiprofen in children aged 6 months to 13 years. Flurbiprofen permeates into the CSF readily and thus, may have potent CNS analgesic and antipyretic action. More data are needed on PK of flurbiprofen in neonates and in younger infants, and on the safety, efficacy and targeted analgesic concentrations of flurbiprofen in children.

Competing interests

There are no competing interests to declare.

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