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Cerebrospinal Fluid Distribution of Ibuprofen After Intravenous Administration in Children

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

BACKGROUND. Ibuprofen is the most commonly used nonsteroidal, antipyretic, anti-inflammatory analgesic in children. Nonsteroidal, antipyretic, antiinflammatory analgesics act in both the peripheral tissues and the central nervous system. The central nervous system penetration of ibuprofen has been described in adults but not in children.

OBJECTIVES. Our goals were to investigate the cerebrospinal fluid penetration of ibuprofen in children and evaluate the analgesic plasma concentration of ibuprofen after inguinal surgery in children.

MATERIALS AND METHODS. A total 36 healthy children (25 boys) aged 3 months to 12 years received a single intravenous injection of ibuprofen (10 mg/kg). A paired cerebrospinal fluid and blood sample was obtained 10 minutes to 8 hours after the injection. In children having inguinal surgery, a second blood sample was obtained at the time that the child first had wound pain.

RESULTS. The ibuprofen level was determined in all cerebrospinal fluid and plasma samples. Cerebrospinal fluid concentrations ranged between 15 and 541 μg/L, and the highest concentrations were measured 30 to 38 minutes after dosing. In all cerebrospinal fluid samples collected after 30 minutes, ibuprofen concentration exceeded that of unbound plasma. The plasma analgesic concentrations after inguinal surgery ranged between 10 and 25 mg/L.

CONCLUSIONS. Ibuprofen penetrates the cerebrospinal fluid readily, with peak concentrations attained 30 to 40 minutes after intravenous injection of a 10 mg/kg dose. The plasma analgesic concentration after inguinal surgery with spinal anesthesia is 10 to 25 mg/L.

www.pediatrics.org/cgi/doi/10.1542/peds.2007-0064

doi:10.1542/peds.2007-0064

Key Words
ibuprofen, cerebrospinal fluid, pharmacology, pharmacokinetics, analgesic concentration, child, infant

Abbreviations
NSAID—nonsteroidal antiinflammatory drug
CNS— central nervous system
PGE_2— prostaglandin E_2
CSF— cerebrospinal fluid
PACU—postanesthesia care unit
BCSFB— blood-cerebrospinal fluid barrier

Accepted for publication Mar 14, 2007

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

IBUPROFEN HAS A good record of efficacy and safety in children,[1] and thus it is the most commonly used nonsteroidal antiinflammatory drug (NSAID) for the treatment of inflammation, fever, and pain. Ibuprofen can be used even for the most vulnerable patient populations; recently intravenous ibuprofen was approved for the treatment of symptomatic patent ductus arteriosus in preterm infants.[2]

After surgery, ibuprofen, like other NSAIDs, is a good analgesic.[3] In the treatment of mild and moderate pain, NSAIDs are sufficient as a sole agent, and effective pain relief is achieved with smaller doses of opioids when NSAIDs are used for background analgesia in severe pain.[4] However, the analgesic plasma concentration of ibuprofen has not been established in children.

Ibuprofen is thought to act both peripherally and in the central nervous system (CNS). NSAIDs reduce pain and inflammation by inhibiting the cyclooxygenase enzyme at the site of tissue damage. Moreover, NSAIDs also seem to have analgesic effects at the spinal cord and other regions in the CNS.[5,6] At the spinal cord cyclooxygenase-inhibition reduces the production of prostaglandin E_2 (PGE_2), which is an important mediator of spinal hyperalgesia.[7] The antipyretic effect of ibuprofen is mediated in the hypothalamus.[8] Similarly, adverse effects associated with ibuprofen are both peripheral and central in origin. Rare peripheral adverse effects include gastrointestinal symptoms and bleeding, renal failure, fluid retention and rash,[9] and very rare CNS adverse effects include dizziness, vertigo, malaise, fatigue, lethargy, depression, agitation, headache, blurred vision, and aseptic meningitis.[10]

Ibuprofen must penetrate the CNS to have central effects, whether beneficial or detrimental. The penetration of ibuprofen enantiomers into cerebrospinal fluid (CSF) was evaluated in adults,[11] but we are unaware of any reports concerning ibuprofen CSF penetration in children. This study investigated CSF penetration after intravenous injection of ibuprofen 10 mg/kg in healthy children undergoing surgery in the lower part of the body with spinal anesthesia. Furthermore, because the analgesic concentration of ibuprofen was not previously described in children, the secondary aim was to evaluate the analgesic concentration of ibuprofen in children undergoing surgery on the inguinal region.

METHODS

The study was open and prospective, the protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (No. 120/2004), the Finnish National Agency for Medicines was notified (No. 161/2004), the trial was recorded in the EudraCT database (No. 2004-001702-27), and it was conducted in accordance with the latest revision of the Declaration of Helsinki.

All children having surgery at the Kuopio University Hospital, who were between 3 months and 12 years of age, who had surgery after which NSAIDs are commonly used for background analgesia and for which spinal anesthesia with sedation was planned, were candidates for inclusion in the study. They were not admitted to the study if any of the following exclusion criteria were present: (1) informed, written consent not obtained from parents or assent not obtained from the child (if old enough to understand the study protocol); (2) any concomitant disease, American Society of Anesthesiologists' Physical Status of ≥3; and (3) any contraindication to ibuprofen (eg, allergy to ibuprofen or any excipients, aspirin-sensitive asthma, gastric or duodenal ulcer, cardiac, hepatic or renal insufficiency, hemorrhagic diasthesis, thrombocytopenia, surgery with a risk of significant hemorrhage).

The children (28 of 36) were premedicated with buccal midazolam (0.375 mg/kg up to 7.5 mg) and ketamine (1.25 mg/kg up to 25 mg) 15 to 30 minutes before anesthesia. All children were sedated before spinal anesthesia ($n = 30$) or combined spinal-epidural anesthesia ($n = 6$).

The children received a single intravenous injection of ibuprofen 10 mg/kg (Ibuprof von ct Amp. 133 mg/mL, lot No. F26775, expiration date July 2008; ct-Arzneimittel Gmbh, Berlin, Germany) diluted in 20 mL of 0.9% saline over 5 minutes, given 10 minutes to 8 hours before lumbar puncture for spinal anesthesia. The injection was given into a cannula inserted in a dorsal hand vein. One milliliter of CSF was collected into a polypropylene tube during lumbar puncture before the injection of local anesthetic. Within 5 minutes, an indwelling catheter was inserted in a dorsal foot vein and a 3-mL blood sample was obtained.

After the surgery, children were transferred to the postanesthesia care unit (PACU) for monitoring of vital signs, pain, and adverse events. The pain intensity at rest and with light pressure (20 N) on the wound area was assessed every 15 minutes by educated research nurses on an 11-point numeric rating scale (0 = no pain; 10 = worst possible pain). For children having inguinal surgery, a second 3-mL blood sample was obtained for the estimation of the analgesic concentration of ibuprofen when first assessed as having wound pain. Thereafter the children received paracetamol (acetaminophen) 15 mg/kg and/or ketoprofen 1 mg/kg intravenously, and pain was assessed and recorded hourly. For rescue analgesia children in pain (pain score at rest ≥3 of 10 or with 20-N compression ≥5 of 10) were provided fentanyl 1 μg/kg intravenously or oxycodone 0.05 mg/kg intravenously.

Analytical Methods

Blood samples were collected into heparinized tubes. Plasma was obtained by centrifugation at 3000 g at 20°C for 10 minutes. The plasma was divided into 2 polypro-

pylene tubes to obtain 2 samples of at least 0.5 mL each. The plasma and CSF were stored at −80°C and protected from light.

Ibuprofen concentrations were measured from CSF, plasma, and protein-free plasma by gas chromatography with mass spectrometric detection. Protein-free plasma was obtained by ultrafiltration. Ibuprofen was isolated from CSF (200 μL), plasma (100 μL) and protein-free plasma (50 μL) by solid-phase extraction. Analytes were quantified with selected ion monitoring at m/z 205 and 294 for pentafluorobenzyl derivative of ibuprofen and diclofenac (internal standard), respectively. The range of the method was 4 to 225, 1000 to 70 000, and 7 to 1800 ng/mL for CSF, plasma, and protein-free plasma samples, respectively. The concentration below the range of method (the unbound plasma concentration of patient 11) was extrapolated from the calibration curve, and the concentrations exceeding the upper quantification limits were reanalyzed from diluted samples. Accuracy, recovery, and intra-day precision of the method was studied at 3 different concentration levels in each range of the method. The accuracy and recovery of the methods ranged between 80% to 120% and 80% to 95%, respectively. The intraday precision at the lowest level of quantitation was <20% (coefficient of variation percentage).

Statistical Methods

No formal sample size calculation was performed but a sample of 30 to 40 children was considered to provide sufficient information on CSF penetration of ibuprofen in children. Data were entered and analyzed with SPSS 13.0 for Windows (SPSS Inc, Chicago, Il). Because there was no control group, descriptive results (number of cases or median with range) are presented. Correlations between ibuprofen concentrations and patient characteristics were tested with the Pearson Correlation test. A P value of .05 was considered as the limit of statistical significance. The trend line of CSF–ibuprofen was generated by applying locally weighted smooth regression (kernel function: Epanechnikov and points to fit: 50%).[12]

RESULTS

A total of 38 children were found eligible and were asked to participate the study, but parents of 1 child refused to consent and 1 child was excluded from the study as the operation was postponed. Hence, the study group consisted of 36 healthy children. There were no protocol deviations likely to interface with the study results. All the children received the study medication as defined in the protocol, and all CSF and plasma samples were collected as defined in the protocol.

The study group consisted of 36 children (25 boys and 11 girls) scheduled for herniotomy (19 children), orthopedic (7 children), genitourinary (6 children), and plastic surgery (4 children), all to be performed under spinal anesthesia. The patient characteristics, individual sampling times, and ibuprofen concentrations are presented in Table 1.

Ibuprofen was determined in all CSF samples, and the concentrations ranged between 15 and 541 μg/L (median: 182 μg/L; Fig 1). There was no significant correlation between ibuprofen CSF concentration and children's age, weight, height or gender (data not shown).

Total plasma concentration of ibuprofen ranged between 1.5 and 89 mg/L (median: 43 mg/L), and unbound plasma concentrations (eg, concentrations in protein-free plasma) ranged between 4.8 and 604 μg/L (median: 72 μg/L; Fig 2). Ibuprofen was highly protein bound and the unbound/total plasma concentration ratio ranged between 0.0008 and 0.0068 (0.0020).

While the CSF and total plasma concentration ratio ranged between 0.0015 and 0.021 (median: 0.0055), the CSF and unbound plasma concentration ratio ranged between 0.42 and 8.6 (3.0). The CSF ibuprofen concentration was higher than the unbound plasma concentration (ie, the ratio was above 1) in all samples taken after 30 minutes. There was a positive correlation between sampling time and concentration ratio of CSF/total plasma and CSF/unbound plasma ($r = 0.66$, $P = .001$ and $r = 0.39$, $P = .018$, respectively).

The children with inguinal surgery developed wound pain at 186 to 266 minutes (median: 213 minutes) after ibuprofen injection and at 57 to 231 minutes (138 minutes) after the end of surgery. The total and unbound plasma concentrations of ibuprofen obtained at the onset of wound pain ranged from 10 to 25 mg/L (21 mg/L) and 15 to 157 μg/L (26 μg/L), respectively.

For pain treatment in the PACU, 25 children received ketoprofen and 3 children a second dose of ibuprofen. Six children had an epidural infusion. Ten children had significant pain in the PACU (numeric rating scale >3 of 10 at rest or >5 of 10 with 20-N compression), and they were given intravenous fentanyl ($n = 6$) or oxycodone ($n = 4$) for rescue analgesia.

There were no serious or unexpected adverse events. Seven children developed mild adverse effects: 3 children were agitated, 2 children had nausea, 1 child vomited, and 1 child was coughing. None of the patients complained of pain during ibuprofen injection.

DISCUSSION

Surgery induces pain and inflammatory responses, and recent data indicates that cyclooxygenase 1 and 2 are both important contributors in the pathophysiological process at the spinal cord.[6] After surgery, both the spinal cord cyclooxygenase 1 expression and CSF PGE_2 concentration increase. Clinical data indicates that, in the acute phase of postsurgical pain, nonselective cyclooxygenase inhibitors (including ibuprofen) are more efficient than cyclooxygenase 2 inhibitors,[13,14] and in experimental studies, postoper-

TABLE 1 **Ibuprofen Concentrations in CSF and Plasma (Unbound and Total) and Concentration Ratios From Each Patient**

Patient No.	Sampling Time, min	CSF Concentration, μg/L	Unbound Plasma Concentration, μg/L	Total Plasma Concentration, mg/L	CSF/Unbound Plasma Ratio	CSF/Total Plasma Ratio	Age, mo	Height, cm	Weight, kg	Gender
20	10	114	268	75	0.42	0.0015	42	100	14	Female
33	12	150	160	64	0.94	0.0023	91	137	31	Male
35	14	185	132	72	1.4	0.0026	21	84	14	Female
37	14	144	158	42	0.91	0.0034	79	124	24	Male
3	21	273	137	57	2.0	0.0048	7	69	10	Male
1	27	149	330	72	0.45	0.0021	117	136	29	Male
21	27	179	80	50	2.2	0.0036	22	83	12	Female
8	28	208	258	71	0.81	0.0029	103	135	36	Male
5	30	355	604	89	0.59	0.0040	19	77	10	Male
18	30	541	199	70	2.7	0.0077	5	66	9	Male
7	38	406	174	71	2.3	0.0057	30	84	14	Female
29	39	237	205	73	1.2	0.0032	126	154	50	Male
26	43	189	90	52	2.1	0.0036	16	80	10	Male
9	50	268	179	55	1.5	0.0049	149	146	34	Male
30	52	296	64	34	4.6	0.0088	27	92	14	Male
36	57	191	75	45	2.5	0.0042	30	90	14	Male
6	63	231	41	37	5.7	0.0062	14	78	12	Male
22	66	234	87	49	2.7	0.0048	80	118	30	Male
31	68	270	134	51	2.0	0.0052	52	103	17	Male
32	71	265	197	44	1.3	0.0060	117	139	40	Male
2	82	243	69	39	3.5	0.0062	8	67	8	Female
14	85	215	64	44	3.3	0.0049	63	104	15	Female
19	89	172	34	37	5.0	0.0047	49	102	15	Female
16	93	218	33	41	6.7	0.0053	12	96	10	Male
13	103	143	22	18	6.5	0.0081	5	57	6	Female
15	110	75	16	18	4.6	0.0041	7	68	8	Female
27	141	100	35	18	2.9	0.0054	8	75	11	Male
17	157	96	51	16	1.9	0.0062	56	109	20	Male
12	160	169	20	16	8.6	0.011	3	64	7	Female
34	169	87	18	20	4.9	0.0044	38	105	18	Male
10	211	78	17	10	4.6	0.0075	134	153	54	Male
24	255	36	9.2	11	3.9	0.0034	45	110	19	Female
23	260	40	20	9.4	2.0	0.0042	78	125	29	Male
4	280	37	22	3.7	1.7	0.0099	33	90	15	Male
25	335	15	7.1	2.9	2.0	0.0049	110	140	51	Male
11	469	30	4.8[a]	1.5	6.4	0.021	77	125	29	Male
Minimum	10	15	4.8	1.5	0.42	0.0015	3	54	6	
Maximum	469	541	604	89	8.6	0.021	149	154	54	
Median	67	182	72	43	2.3	0.0049	40	101	15	

[a] Below the limit of quantification, extrapolated from the calibration curve.

ative pain can be relieved effectively with intrathecal cyclooxygenase 1 inhibitors.[6,15] In clinical work, NSAIDs are not administered intrathecally; therefore, we decided to study ibuprofen concentrations in CSF after intravenous injection in healthy children who were undergoing surgery.

The present study indicates that ibuprofen readily penetrates the CSF in children. In the earliest samples taken 10 to 15 minutes after ibuprofen injection, the CSF concentrations were above 100 μg/L, and the highest ibuprofen concentrations in CSF, 541 and 406 μg/L, were detected 30 to 38 minutes after injection. Thereafter, the ibuprofen concentrations in CSF declined relatively fast, and in all except 1 CSF sample collected >2 hours after the injection ibuprofen concentrations were <114 μg/L, the CSF concentration in the first sample at 10 minutes after injection. The decline in the plasma concentrations of ibuprofen occurred earlier, and in all 27 CSF samples collected later than 30 minutes after the injection, ibuprofen concentrations in CSF were threefold to fourfold higher than the unbound plasma concentrations.

We are unaware of any other studies of CNS penetration of ibuprofen in children. In adults, Bannwarth et al[11] have described the CSF concentrations after 800 mg of ibuprofen by mouth. They reported an average peak (*R*)- and (*S*)-ibuprofen CSF concentration of 168 and 315 μg/L, respectively. The calculated total ibuprofen concentration in CSF was 483 μg/L, which is similar to the value of 541 μg/L in the present study. After oral administration the peak CSF ibuprofen concentration was attained in 3 hours in contrast to a peak at 30 minutes in the present study, which indicates that when a rapid spinal analgesic action is

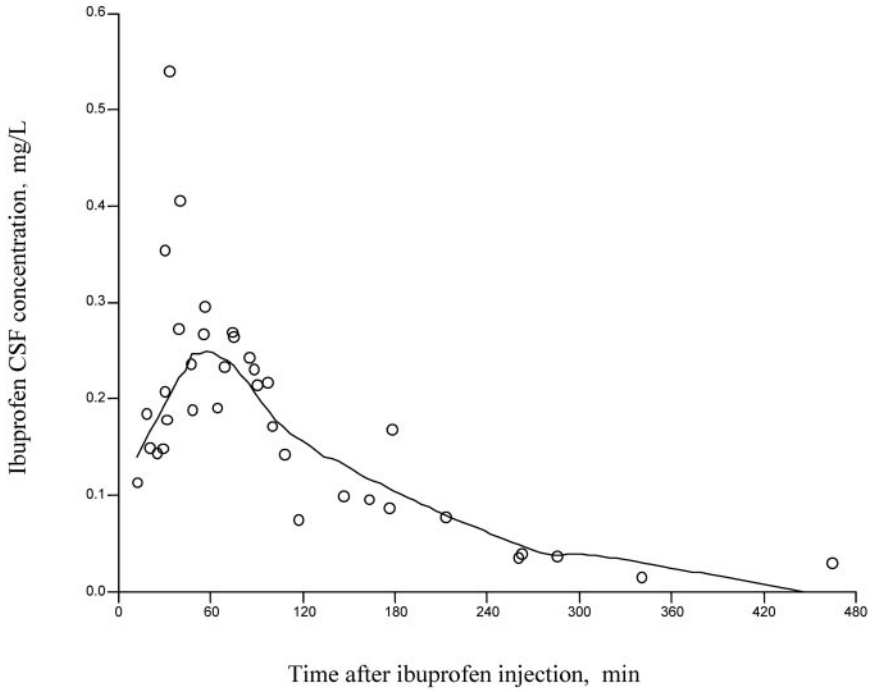

FIGURE 1
CSF ibuprofen concentrations after a single intravenous injection of ibuprofen 10 mg · kg^{-1} and locally weighted smooth-regression trend line.

desired, the first dose of ibuprofen should be given intravenously.

The secondary aim of our study was to estimate the analgesic concentration of ibuprofen. The plasma ibuprofen concentration at the onset of pain ranged between 10 and 25 mg/L with a median concentration of 21 mg/L, which is consistent with that reported in adults.[16,17] After intravenous ibuprofen 10 mg/kg, these plasma concentrations were sustained for 2 to 4 hours. Therefore, the common practice in day-case surgery of administering a second dose of ibuprofen at discharge, 3 to 4 hours after the first dose, seems to be supported by the pharmacokinetic data.[3,4] However, it should be noted that the children in the present study had spinal anesthesia with bupivacaine, which may have affected the pain perception during recovery. Studies have indicated that children who have spinal anesthesia may have less pain than those who receive inhalation anesthesia.[18]

To our knowledge, this was the first attempt to estimate the analgesic concentration of ibuprofen in children. In adults, a similar analgesic concentration has been obtained in patients having dental surgery and in volunteer subjects using a low pH-pain model. Laska et al[16] administered 400- to 800-mg ibuprofen tablets to adults with moderate or severe pain after third molar extraction. Half of the patients had complete pain relief with a serum concentration of 26 mg/L. In a volunteer study, Steen et al[17] used a cutaneous acidosis pain model to evaluate the analgesic efficacy of 800-mg ibuprofen tablets. Significant pain relief was observed 25 minutes after drug ingestion with a mean ibuprofen concentration of 25 mg/L.

Although ibuprofen could be detected in the earliest CSF samples, the CSF concentrations were only 1 of 100 to 1 of 1000 of those in plasma. Physicochemical characteristics of drugs, particularly lipophilicity and degree of ionization at the absorption site, affect their ability to penetrate the CSF and the CNS. Most NSAIDs including ibuprofen are lipophilic and their unionized forms have logP (the logarithmic octanol-water partition coefficient) values in the range of 1 to 3. Because of their high lipophilicity, NSAIDs would be expected to pass through the blood-brain barrier and the blood-CSF barrier (BCSFB) readily by passive diffusion. However, ibuprofen penetration to CSF is limited at physiologic pH (7.4) as it is almost totally ionized (99%).[19] On the other hand, the apparent partition coefficient value of ibuprofen at a pH of 7.4 is 1.1,[20] making it capable of entering CSF readily.

Another possible factor restricting the penetration of ibuprofen in CSF is its high degree of protein binding in plasma. Ibuprofen is over 99% bound to plasma proteins, and it is generally believed that only the unbound fraction of drug in plasma is able to pass through biological membranes. Other possible factors restricting the CSF penetration of ibuprofen are efflux mechanisms at the BCSFB, such as organic anion transport systems and multidrug resistance proteins.[21–23]

There seems to be significant differences in CNS penetration and CSF pharmacokinetics between different nonopioid analgesics. We have previously studied the CSF penetration of 2 other NSAIDs, ketoprofen and indomethacin, as well as paracetamol (acetaminophen) in children.[24–26] Like ibuprofen, both ketoprofen and in-

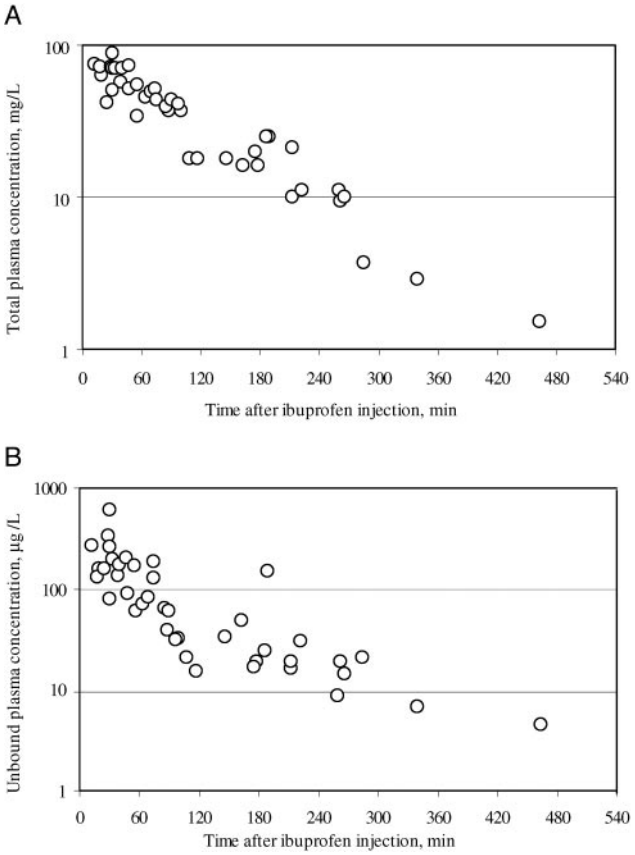

FIGURE 2
Total (A) and unbound (B) plasma concentrations after a single intravenous injection of ibuprofen 10 mg • kg^{-1}. The figures are shown in logarithmic scale.

domethacin have high affinity to plasma proteins (~99%), and significantly lower CSF concentrations than those in plasma were found with both drugs. Ketoprofen (1 mg/kg) (ie, a 10-fold smaller dose than that of ibuprofen) resulted in 20- to 60-fold smaller CSF concentrations (1.4–24 μg/L) when compared with the present study with ibuprofen.[24] Increasing CSF ketoprofen concentrations were observed through the 67-minute study period, similar to the pattern with ibuprofen in the present study. However, during the duration of the study, ketoprofen concentrations in CSF did not equal the unbound plasma concentrations (except in 1 sample at 58 minutes), whereas in the present study all ibuprofen CSF concentrations at 30 minutes or more after administration were higher than the unbound plasma concentrations. We assume that ibuprofen penetrates the CSF readily because it is more lipophilic ($logP_{7.4}$: 1.1) than ketoprofen ($logP_{7.4}$: −0.09). However, it remains unclear whether ibuprofen is eliminated from CSF faster than ketoprofen, which might explain the longer clinical analgesic action of ketoprofen when compared with ibuprofen.[3,4]

Intravenous indomethacin 0.35 mg/kg (ie, a 30-fold smaller dose than that of ibuprofen) resulted in 50- to 100-fold smaller CSF concentrations (0.2–5.0 μg/L), when compared with the present study using ibuprofen.[25] With indomethacin there was a more significant interindividual variation in the CSF concentrations than that which we observed with ibuprofen, and no temporal trend line could be detected with indomethacin, unlike ibuprofen. We expected similar CSF pharmacokinetics with indomethacin as its lipophilicity ($logP_{7.4}$ 0.9) and protein binding are comparable to ibuprofen. There seems to be some differences in the adverse effects of the 2 compounds. Indomethacin was associated with central adverse effects in some children[25] whereas a single dose of ibuprofen was found to be well tolerated, as also shown by Lesko and Mitchell[1] in a large-scale study.

In our previous study with a 1.5-fold dose of paracetamol (acetaminophen), 15 mg/kg, the extent of BCSFB penetration was greater.[26] With paracetamol the CSF concentrations were 50 to 500-fold higher (1.3–18 mg/L) than ibuprofen in the current study. After intravenous paracetamol CSF concentrations peaked later, during the second hour after injection, whereas with ibuprofen the highest concentrations were measured at 30 to 40 minutes. Whereas paracetamol concentrations were higher in CSF than in plasma after 1 hour, ibuprofen concentrations in CSF were 0.15% to 1.1% of plasma concentrations at all times, and CSF concentrations exceeded the unbound plasma concentrations after 30 minutes. Paracetamol is not significantly bound to plasma proteins and we assume that, therefore, it can reach higher concentrations in CSF than highly protein bound NSAIDs.

CONCLUSIONS

Ibuprofen readily penetrates into the CSF in children. The peak CSF concentrations are attained 30 to 40 minutes after intravenous administration, and thereafter the CSF concentrations are higher than the unbound plasma concentrations. The analgesic concentration after inguinal surgery in children is between 10 to 25 mg/L.

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