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.
IBUPROFEN HAS a good record of efficacy and safety in children, 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.

After surgery, ibuprofen, like other NSAIDs, is a good analgesic. 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. 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. At the spinal cord cyclooxygenase-inhibition reduces the production of prostaglandin E2 (PGE2), which is an important mediator of spinal hyperalgesia. The antipyretic effect of ibuprofen is mediated in the hypothalamus. 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, and very rare CNS adverse effects include dizziness, vertigo, malaise, fatigue, lethargy, depression, agitation, headache, blurred vision, and aseptic meningitis.

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, 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 diathesis, thrombocytopenia, surgery with a risk of significant hemorrhage).

The children (28 of 36) were premedicated with buc- cal 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 fenta- nyl 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 quantification 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 in 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-
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 al11 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

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

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sampling Time, min</th>
<th>CSF Concentration, μg/L</th>
<th>Unbound Plasma Concentration, μg/L</th>
<th>Total Plasma Concentration, mg/L</th>
<th>CSF/Unbound Plasma Ratio</th>
<th>CSF/Total Plasma Ratio</th>
<th>Age, mo</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>Gender</th>
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<td>30</td>
<td>48*</td>
<td>1.5</td>
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<td>4.8</td>
<td>1.5</td>
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<td>89</td>
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<td>182</td>
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<td>43</td>
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<td>15</td>
<td>101</td>
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</tbody>
</table>

*Below the limit of quantification, extrapolated from the calibration curve.
desired, the first dose of ibuprofen should be given intra-
venously.

The secondary aim of our study was to estimate the
analgesic concentration of ibuprofen. The plasma ibu-
profen concentration at the onset of pain ranged be-
tween 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 anes-
thesia 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 esti-
mate the analgesic concentration of ibuprofen in chil-
dren. 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
al16 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 al17 used a cutaneous acidosis pain model
to evaluate the analgesic efficacy of 800-mg ibuprofen
tables. Significant pain relief was observed 25 minutes
after drug ingestion with a mean ibuprofen concen-
tration 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 char-
acteristics 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, ibupro-
fen 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 pro-
teins, and it is generally believed that only the unbound
fraction of drug in plasma is able to pass through biolog-
ical 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 pen-
etration 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-

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**FIGURE 1**

CSF ibuprofen concentrations after a single intra-
venous injection of ibuprofen 10 mg·kg⁻¹ and locally
weighted smooth-regression trend line.
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. Increasing CSF ketoprofen concentrations were observed through the 67-minute study period, similar to the pattern with ibuprofen. With indomethacin the CSF concentrations were 50 to 100-fold smaller CSF concentrations (0.2–5.0 μg/L), when compared with the present study using ibuprofen. 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 (logP7.4 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 whereas a single dose of ibuprofen was found to be well tolerated, as also shown by Lesko and Mitchell 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. 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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Pediatrics 2007;120;e1002
DOI: 10.1542/peds.2007-0064

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