Use of nonsteroidal anti-inflammatory drugs in infants. A survey of members of the Association of Paediatric Anaesthetists of Great Britain and Ireland

NICHOLAS EUSTACE FCARCSI MMEDSCI, BRENDA O’HARE FFARCSI DCH MRCPI

Department of Anaesthesia and Critical Care Medicine, Our Lady’s Hospital for Sick Children, Crumlin, Dublin, Ireland

Summary

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as perioperative analgesics. Many are currently used off label. Diclofenac is currently licensed for use in children over 1 year of age for the treatment of juvenile rheumatoid arthritis, while ibuprofen is licensed for use in children weighing over 7 kg. The dose and interval in children is currently extrapolated from adult studies, as the pharmacokinetic (PK) and pharmacodynamic (PD) data are lacking in infants.

Methods: A postal questionnaire was sent to members of the Association of Paediatric Anaesthetist of Great Britain and Ireland seeking to clarify members’ prescribing patterns of NSAIDs, especially in infants. Information regarding the choice of NSAIDS, route of administration, lower age limit, dose interval, dose and practice in two specific perioperative contexts (adenotonsillectomy and open heart surgery) was sought.

Results: The response rate was 80%. NSAIDs are used by 86% of responders in infants. Diclofenac is most commonly used intraoperatively (78%); while ibuprofen (73%) was used more frequently postoperatively. NSAIDs are used by 21% of respondents in ICU. Commonest routes of administration were oral (81%) and rectal (80%), rarely intravenously (9%). The commonest dose for diclofenac is 1 mg kg⁻¹ (59%); the dosing schedule employed being 8 hourly in 53% of cases. NSAIDs are used by 57% of responders as part of their analgesic regime for adenotonsillectomies.

Conclusion: Members of the Association of Paediatric Anaesthetists of Great Britain and Ireland commonly prescribe NSAIDs in infants. This is despite the dearth of PK and PD data in this age group.

Keywords: infants; nonsteroidal anti-inflammatory drugs; survey
**Introduction**

Many therapeutic agents used in pediatric medical practice are not licensed for use in this age group. This situation has arisen as drug companies have not been obliged to provide pediatric-dosing information (1). Licensing of any drug or biologically active compound for use in pediatrics requires the provision of pediatric pharmacokinetic (PK) and safety data. Currently, the Food and Drug Administration (FDA) require all biologically active agents to provide pediatric-dosing information, where they may be of possible beneficial use in children, in order to be licensed (2). Until recently there was no obligation on pharmaceutical companies to provide this pediatric data. It was possible to avoid providing it by stating that use of the particular product was not recommended in infants and children. This occurred, as there was often little financial incentive to the companies to engage in this expensive research. Many are therefore used ‘off label’ in children. This lack of information then exposes children to adverse drug reactions and inappropriate dosing. Cote and Alexander (3) describe cases where a physician has been subject to litigation following the prescription of an unlicensed drug. Shirkey in 1968 (4) coined the phrase ‘therapeutic orphans’ to describe this phenomenon.

Off label use is common in pediatrics, in a recent study Conroy et al. 33% of analgesic hospital prescriptions in children on both surgical and medical wards were off label. The commonest prescribed analgesics were paracetamol, ibuprofen, codeine and diclofenac. The commonest cause of ‘off label’ use included the dose, route, age and indication (5). Drugs are used ‘off label’ in infants despite the lack of PK, pharmacodynamic (PD) and safety data in this population. Common examples include antibiotics and analgesics. Ibuprofen is licensed for children over 7 kg in Britain and Ireland but is used in children smaller than this, while intravenous morphine is not licensed for use in children despite published PK data. Indomethacin, which is used in premature babies for patent ductous arteriosis closure, is unusual in that it is licensed for use in premature infants. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used as part of multimodal analgesic regimen in infants (6) and children (7). They have the advantage of relatively few side effects and are useful in day case surgery. Doses prescribed are derived from adult kinetic studies. This is in contrast to other analgesics such as morphine where pediatric and infant PK data is available which allows rational doses and intervals to be prescribed.

There is a paucity of information on the NSAID prescribing practices of pediatric anesthetists in infants. In order to examine this, we sent a postal questionnaire to members of the Association of Paediatric Anaesthetists of Great Britain and Ireland. As there has been debate in the literature recently about the use of NSAIDs, as part of the anesthetic for adenotonsillectomies, we also questioned members about this issue.

**Methods**

A list of current members was requested from the Association and a single page anonymous postal questionnaire was sent to each member over a 6-month period July to December 2003. The survey was sent to all members working within Great Britain and Ireland and also to some European members, with a cover letter explaining the aims of the questionnaire. As we could not consistently provide stamped addressed envelopes to this latter group (European members) the number of questionnaires sent to this group was restricted. The questionnaire was piloted among members of our department.

In the questionnaire we sought information to try and establish prescribing habits for NSAIDs in infants (see Appendix).

**Results**

Four hundred and eighteen surveys were sent, 337 replies were received (80.6%). Twenty-three responders were retired. Of those still in practice, NSAIDs are used by 86% in infants. Diclofenac is the most commonly used NSAID intraoperatively (78.6%), while ibuprofen (73.6%) is used more commonly postoperatively. Ketoprofen/Ketorolac is used by 1%. NSAIDs are used by 21% of responders in ICU (Figure 1). The most popular routes of administration are oral (81.5%) and rectal (80.6%); rarely intravenously (9.2%) (Figure 2). NSAIDs are prescribed in infants <1 month of age.
by 4% of responders; 1–3 months by 19%; 4–6 months by 48%; 6–12 months by 78% and 90% prescribe them in children >1 year of age (Table 1).

The most commonly prescribed dose of diclofenac is 1 mg·kg\(^{-1}\) (59%); 2 mg·kg\(^{-1}\) (19%) and 3 mg·kg\(^{-1}\) (1.3%). The interval between doses prescribed varies between 6 (3.5%), 8 (53%) 12 (11%) and 18 hourly (1.3%) (Figure 3). Fifty-seven per cent of responders use NSAIDs as a component of the analgesic regime for adenotonsillectomies; diclofenac in particular is used by 44% of members. NAIDs are used by 19 (5.6%) members in ICU following cardiac surgery.

**Discussion**

The primary finding of this study is that NSAIDs are widely used among members in infants, despite the paucity of PK and PD data for these agents when used in infants (1). Surveys such as this are always subject to bias, i.e. members who use NSAIDs are more likely to respond than those who do not. An 80% response rate to our survey is very high and therefore, represents the practice of the majority of members of the association. It compares favorably with previously published surveys with response rates of 65% by Orliaguet et al. (8) and 72% by Williams et al. (9). A high response rate reduces the effect of bias and therefore, this survey should reflect the practice of the majority of members of the Association of Paediatric Anaesthetists of Great Britain and Ireland. The commonest routes of administration in our survey were oral and rectal. Some members (9.2%) give NSAIDs intravenously.

Our survey has demonstrated that there is broad consensus among members as to appropriate diclofenac dosing interval (eight hourly) and dose (1 mg·kg\(^{-1}\)). However, this is an empiric consensus. Based on PK data from our group in older children, a higher dose (2 mg·kg\(^{-1}\)) results in PK values that are acceptable and safe (10). The BNF for children recommends a dose of up to 3 mg·kg\(^{-1}\)·day\(^{-1}\) in children older than 6 months (11). NSAIDs are prescribed in infants under the age of 6 months by

---

**Table 1**

Cumulative nonsteroidal anti-inflammatory drug prescription patterns in infants by APA members

<table>
<thead>
<tr>
<th></th>
<th>&lt;1 month</th>
<th>1–3 months</th>
<th>4–6 months</th>
<th>6–12 months</th>
<th>&gt;1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.8%</td>
<td>19.4%</td>
<td>47.7%</td>
<td>78%</td>
<td>90.4%</td>
</tr>
</tbody>
</table>

© 2007 The Authors
nearly 48% of responders and by 80% in infants <1 year of age.

Pharmacokinetic studies allow appropriate dose scheduling as it describes the dose per unit weight to be prescribed and also the appropriate interval. Infants have rapidly developing enzyme systems therefore using weight alone when prescribing may be inappropriate (12). Anderson et al. recommends the use of an allometric \( \frac{3}{4} \) power model, standardized to a 70-kg person, in children older than infants when describing PK variables such as volume of distribution. This allows direct comparison with adult PK values and makes the effect of age rather than weight clearer. Anesthetists currently prescribe on a per kilogram basis and this will be difficult to change, but both age and weight should be used when prescribing in children and infants (13). Two recent reviews by Litalien and Davies both highlighted the paucity of kinetic data for NSAIDs in children. Litalien concludes that NSAIDS are safe and effective analgesics and anti-inflammatory agents when used in children but that PK studies are required in small children and infants (1). Also the therapeutic blood concentrations need to be defined (14). Davies also comments on the limited information on the concentration effect relationship of diclofenac and also the toxicologic relevance of diclofenac PK. With respect to children, Davies comments on the fact that children may require more frequent doses to maintain clinical responses and current therapeutic regimens are derived from adult PK (14). It is likely that children with their larger volume of distribution and clearance require higher doses per kilogram and more frequent administration (1,14). It is not clear what the optimum dose regime for infants is, as there is little PK data available. As both these reviews suggested, the target level required to provide analgesia or the level at which toxicity occurs is unknown.

Interestingly NSAIDs are used by the majority of responders, in children undergoing adenotonsillectomies, despite the recommendations of a recent meta analysis (15). The conclusion of this study by Maret et al. was that NSAIDs were unsafe for use in children undergoing adenotonsillectomies due to the risk of bleeding. This meta analysis included studies not designed to measure complications of NSAID when used for adenotonsillectomies and also included studies investigating Ketorolac, a NSAID which has been associated with bleeding complications (16). Diclofenac, which is used by most of the members, does not have the same magnitude of effect on platelet function (17,18). In the study by Niemi et al., diclofenac impaired platelet function to a lesser extent than Ketorolac or Ketoprofen, especially on adrenaline induced platelet aggregation. In the same study, diclofenac did not alter bleeding time (18). We have previously described the lack of effect of diclofenac on thromboelastography following adenotonsillectomy (19). In his recent review, Anderson (12) came to the same conclusion.

The exact timing of diclofenac administration when used for adenotonsillectomy was not requested. It is possible that some members may wait for any surgical bleeding to have stopped before giving diclofenac at the end of the procedure. The advantage of diclofenac use in this situation was also highlighted by Lonnqvist and Morton in their recent review (7). Only 17 members use NSAIDs in ICU following cardiac surgery. Most use NSAIDs after the cessation of any bleeding.

Conclusion

Nonsteroidal anti-inflammatory drugs are routinely prescribed by members of the Association for infants. This use is off label and with minimal data to guide the practice. More PK studies are required in children especially in infants to support their safe and effective use in this population.

References

Appendix

Questionnaire on the use on NSAIDs in infants by members of the Association of Paediatric Anaesthetists of Great Britain and Ireland

Do you use NSAIDS in infants
Yes ☐ No ☐

Which NSAIDs do you use?

<table>
<thead>
<tr>
<th>Intraop.</th>
<th>Postop.</th>
<th>In ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Other please specify

What route of administration do you use

- Oral/NG ☐
- Rectal ☐
- IV ☐

Will you use NSAIDs in

- Newborn ☐
- 1–3 months ☐
- 3–6 months ☐
- 6–12 months ☐
- >1 year ☐

Other please specify

If diclofenac what time interval do you leave between doses?

- 6 h ☐
- 8 h ☐
- 12 h ☐
- 18 h ☐

Accepted 9 November 2006
What dose per kg?
1 mg·kg⁻¹  2 mg·kg⁻¹  3 mg·kg⁻¹

Do you use NSAIDs for adenotonsillectomies.
Yes ☐ No ☐ if yes is it diclofenac ☐ or other ☐

If you are using it for open heart surgery, do you use them
At induction ☐
At end of the operation ☐
In the ICU ☐