Pediatric Anesthesia 2004 **14**: 201–217

Review article

Comparing the efficacy of NSAIDs and paracetamol in children

BRIAN J. ANDERSON PhD FANZCA FJFICM

Department of Anaesthesiology, University of Auckland School of Medicine, Auckland, New Zealand

Keywords: nonsteroidal anti-inflammatory drugs; paracetamol; acetaminophen; efficacy; pharmacokinetics; pharmacodynamics; pharmacometrics

Introduction

Paracetamol (acetaminophen) and the nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in children for antipyresis and analgesia. The anti-inflammatory properties of the NSAIDs have, in addition, been used in such diverse disorders as juvenile idiopathic arthritis, Kawasaki disease and cystic fibrosis (1–4). The NSAIDs indomethacin and ibuprofen are also used to treat delayed closure of patent ductus arteriosus (PDA) in premature infants (5). Paracetamol and NSAIDs are often given together for the management of pain or fever. Despite the widespread use of these medications there are few data comparing efficacy of these drugs. The combined effectiveness of paracetamol and a NSAID is insufficiently documented in children and it is unknown if there is synergy or additivity of effect when the two drugs are used together.

Litalien and Jacqz-Aigrain (6) have recently reviewed the risks and benefits of NSAIDs and paracetamol in children. Knowledge of individual drug pharmacokinetics (PK) and pharmacodynamics (PD) is essential to compare effectiveness. Pharmacokinetic age-related changes and covariate effects are poorly documented for many of the NSAIDs. Pharmacodynamic data are often a simple comparison of one drug to another without quantifying effect. There is a paucity of analgesia concentration–effect relationship data in children, although fever control (7–10) and PDA closure (11) relationships are emerging. In order to use these drugs properly, effectiveness data must be balanced against the drugs' safety profiles. Currently this is not carried out and often the safety profile of one NSAID is extrapolated to another.

This current review examines the methods used to compare NSAIDs with paracetamol, the difficulties associated with such comparisons and the impact of drug side effects on dosing regimens in children.

Correspondence to: Dr Brian Anderson, Department of Anaesthesiology, Green Lane Hospital, Auckland, New Zealand (email: briana@adhb.govt.nz).

Mechanism of action

NSAIDs

The NSAIDs are a heterogeneous group of compounds that share common antipyretic, analgesic and anti-inflammatory effects. Their major action is through inhibition of prostaglandin synthesis. The NSAIDs act by reducing prostaglandin biosynthesis through inhibition of cyclo-oxygenase (COX), which exists as two isoforms (COX-1 and COX-2). Most NSAIDs block the function of both isoenzymes to varying degrees (12). The prostinoids produced by COX-1 isoenzyme protect the gastric mucosa,

regulate renal blood flow and induce platelet aggregation. NSAID-induced gastrointestinal (GI) toxicity, for example, is generally believed to occur through blockade of COX-1 activity, whereas the anti-inflammatory effects of NSAIDs are thought to occur primarily through inhibition of the inducible isoform, COX-2.

Paracetamol

Paracetamol (*N*-acetyl-*p*-amino-phenol) has antipyretic and analgesic effects, but is lacking anti-inflammatory effects. The mechanism of action of paracetamol analgesia is multifactorial. It is a potent inhibitor of prostaglandin synthesis within the central nervous system but also acts peripherally by blocking impulse generation within the bradykinin-sensitive chemoreceptors responsible for the generation of nociceptive impulses. Paracetamol is also thought to have an analgesic effect by antagonising *N*-methyl-D-aspartate (NMDA) and substance P in the spinal cord. Analgesic effect also involves an inhibitory action on spinal nitric oxide mechanisms. (13–15).

Efficacy

The clinical effectiveness of a drug depends not on its potency (EC_{50}) but on its efficacy and its ability to reach the relevant receptors. Efficacy reflects the limit of the concentration–response relation on the response axis (16). In therapeutics efficacy denotes the extent or degree of an effect that can be achieved in the intact patient. Pharmacological efficacy does not have the same meaning as effectiveness, although the two terms are sometimes incorrectly used interchangeably. Furthermore, therapeutic efficacy may be limited by the drug's propensity to cause a toxic effect.

Target concentration

Current paediatric dosing of paracetamol or NSAIDs is not based on rigorous efficacy data. Pharmacodynamic data are required to calculate dose. Calculation of the dose for an individual has the strongest theoretical support when based on the target concentration strategy (17). This assumes that a target effect is required and the concentration needed to achieve that effect is predictable from PD factors. The dose is then predicted from the target concentration and pharmacokinetic factors.

Indomethacin target concentrations for PDA closure have been proposed (11) and therapeutic drug monitoring has been recommended to achieve ibuprofen target concentrations in children with cystic fibrosis (18). However, target concentrations for analgesia in children remain poorly defined and some methods used to assess analgesic effectiveness or compare analgesic medications unrefined. Comparisons between NSAIDs and paracetamol often use doses extrapolated from adult data without paediatric PD or PK data to support them.

Methods used to assess the effectiveness of paracetamol or a NSAID

Comparison with local anaesthetic blockade

Inguinal herniotomy has been used as a surgical pain insult to compare postoperative pain relief from a NSAID to caudal bupivacaine (0.2–0.25%) regional blockade. Splinter *et al.* (19) showed similar analgesia after intravenous ketorolac 1 $mg{\cdot}kg^{-1}$ and caudal blockade ($n = 164$). Ryhanen *et al.* (20) demonstrsted children ($n = 240$) given intramuscular diclofenac 1 $mg{\cdot}kg^{-1}$ had improved late postoperative analgesia compared with caudal analgesia. Moores *et al.* (21), using a lower dose of diclofenac 0.25 $mg{\cdot}kg^{-1}$ given rectally, was unable to demonstrate any superiority ($n = 40$).

These data suggest that NSAIDs are an alternative to caudal blockade analgesia after herniotomy, but give little information about quantifying that analgesia. We can imply that the larger dose of intramuscular diclofenac, a route that has a higher relative bioavailability and lower absorption variability than rectal, is more effective for a longer duration than caudal bupivacaine. This is consistent with this drug's known long duration of action, attributable to effect site kinetics. Substantial intra-articular tissue concentrations of NSAIDs are attained after systemic administration and elimination half times are longer in synovial fluid than in plasma, contributing to their effectiveness in arthritis (22,23).

Comparison with morphine

Morphine is accepted as a standard analgesic in children (24,25) and is often used for comparative studies with other analgesic medications. Studies comparing paracetamol or ketorolac (0.75–1 mg·kg^{-1}) with morphine (0.1 mg·kg^{-1}) for analgesia after tonsillectomy (26), strabismus surgery (27) or general surgery have demonstrated similar degrees of analgesia with reduced emesis with some increased bleeding in children given ketorolac.

Morphine, however, may not be the ideal drug to use as a standard because of variability of PK, PD and effect compartment equilibration half-time (T_{eq}) (24,28,29). A concentration–response relationship has not been described. Maunuksela *et al.* (30) attempted to address this issue by titrating either morphine 0.1 mg·kg^{-1} or ketorolac 0.2 mg·kg^{-1} to effect after paediatric surgery. Analgesia was similar in both groups, but children given ketorolac initially required more doses than those children given morphine. This could reflect a lower potency (1 : 1–1 : 3) or a larger T_{eq} for ketorolac. Morphine did not maintain its analgesic effect for as long as ketorolac, again reflecting ketorolac's longer duration of effect.

Direct comparison of NSAIDs with paracetamol

Maunaksela and Olkkola (31) have suggested that 1 mg·kg^{-1} rectal diclofenac = 10 mg·kg^{-1} oral ibuprofen = 40 mg·kg^{-1} rectal paracetamol = 5 mg·kg^{-1} i.v. ketoprofen = 0.5 mg·kg^{-1} i.v. ketorolac. A large number of studies have been performed comparing paracetamol with a NSAID for either analgesia or antipyresis in children. Most show either similar effect or slight superior effect with a NSAID (32–44). One major criticism of such studies is that paracetamol dosing may not be equipotent with that of the NSAID used. Paracetamol doses of 10 mg·kg^{-1} p.o. given either as a single dose (32,36,40) or three to four times daily (35,38,39) may not achieve concentrations associated with analgesia or antipyresis or may achieve these concentrations only after two to three doses (45). Assessment of effect may be made too early – before peak concentrations in the effect compartment are reached (32,33). If the T_{eq} of the NSAID is smaller than that of paracetamol then earlier assessments will favour the NSAID. The duration of effect for the NSAID may be longer than that of paracetamol. Improved analgesia in children given NSAIDs during this later study period will bias results (37). PK vary with age. Clearance in a 1-year-old child is greater than in an 8-year-old child. There are considerable differences in absorption and relative bioavailability between rectal and intravenous formulations. Serum concentrations and consequent effect will vary with age and formulation.

Morphine sparing

Diclofenac and ketorolac are both reported to reduce morphine use in children. Morton *et al.* (46) studied 80 children, aged 5–13 years, who received PCA with morphine after appendicectomy. All patients received morphine 0.1 mg·kg^{-1} before surgical incision and all had wound infiltration with bupivacaine 1 mg·kg^{-1} at the end of surgery. Patients were allocated randomly to receive postoperative analgesia with PCA morphine alone, morphine plus diclofenac 1 mg·kg^{-1} *pr* 8 h, morphine plus paracetamol 15 mg·kg^{-1} *pr* 6 h or morphine plus a combination of both diclofenac and paracetamol. Cumulative morphine consumption was significantly reduced (40%) by concurrent administration of diclofenac but no additive effect of paracetamol was demonstrable with the doses used in the study. The morphine sparing effect of paracetamol was only 17% and not statistically significant compared with morphine alone. Analgesia, as assessed by movement pain scoring, was significantly improved by the addition of diclofenac despite lower morphine consumption. Vetter *et al.* (47) gave 0.8 mg·kg^{-1} of intravenous ketorolac or no additional analgesic at the time of wound closure to surgical candidates 8–16 years. Children given ketorolac used less PCA morphine during the first 12 postoperative hours than did the morphine only group ($P = 0.002$). The morphine plus ketorolac group also reported significantly lower overall VAS pain scores ($P < 0.01$). Oztekin *et al.* (48) have reported similar results with diclofenac in children anaesthetised with remifentanil for tonsillectomy. Diclofenac given rectally reduced pain intensity and postoperative morphine requirements.

These data confirm that NSAIDs in children are effective analgesic drugs, improving the quality of

analgesia, but they do not quantify the effect. It is not possible to develop an understanding of the dose–effect relationship from these data. Nor is it possible to determine if equipotent doses are being compared.

Paracetamol, when used at higher doses (40 or 60 mg·kg^{-1}), does have a clear morphine-sparing effect in day-case surgery in children if administered at the induction of anaesthesia (49). Korpela *et al.* (49) were able to determine a dose–effect relationship. The calculated dose of paracetamol at which 50% of the children not requiring a rescue opioid (ED_{50}) was 35 mg·kg^{-1}.

Number needed to treat

The lack of direct comparisons makes it hard to judge the relative efficacy of analgesics. Relative efficacy may be determined indirectly from comparisons of each analgesic with placebo. A method that converts mean values for pain relief into dichotomous information (number of patients with at least 50% of maximum total pain relief from pain relief scales over 4-6 h) has been validated (50–52). This method has been used to produce a quantitative systematic review of the relative analgesic efficacy of single oral doses ibuprofen and diclofenac in postoperative pain, using the Number Needed to Treat (NNT) as a descriptor of effectiveness (53).

A single dose of ibuprofen 400 mg given to adults had an NNT of 2.7 for at least 50% pain relief compared with placebo (53). This means that one out of every three patients with pain of moderate to severe intensity will experience at least 50% pain relief with ibuprofen, which they would not have had with placebo. It is possible to form a dose–response relationship from these data (Table 1). Rational decisions about dosing equivalence can also be made. Unfortunately paediatric NNT tables are unavailable.

Table 1
NNT for ibuprofen and diclofenac in adults [from Collins *et al.* (53)]

Ibuprofen (mg)	*NNT (95% CI)*	*Diclofenac (mg)*	*NNT (95% CI)*
50	3.6 (2.5–6.1)	25	2.6 (1.9–4.5)
100	5.6 (3.8–9.9)	50	2.3 (2.1–2.7)
200	3.3 (2.8–4)	100	1.8 (1.5–2.1)
400	2.7 (2.5–3)		
600	2.4 (1.9–3.3)		
800	1.6 (1.3–2.2)		

Such adult NNT data support clinical experience showing paracetamol 1000 mg (NNT 4.6, 95% CI 3.8–5.4) has similar analgesic effectiveness to aspirin 1000 mg (NNT 4.0, 3.2–5.4). Ibuprofen 400 mg and diclofenac 50 mg are more effective than paracetamol and aspirin 1000 mg. They are also more effective than several other commonly used analgesics including some with an opioid component, e.g. dextropropoxyphene 65 mg plus paracetamol 650 mg (NNT 4.4, 3.5–5.6), tramadol 100 mg (NNT 4.8, 3.8–6.1) and dihydrocodeine 30 mg (NNT 9.7, 4.5 to >10000) (53).

The 95% confidence levels for some of NNT estimates are broad. One contributor to this range is PK variability. For example, Prescott (54), in a study of 43 adult convalescent patients, reported an 80-fold range in concentrations 1 h after 500 mg tablets. A concentration–response relationship eliminates PK variability contained in the dose–response relationship.

The sigmoid E_{max} model

The relation between drug concentration and effect may be described by a hyperbolic curve according to the equation

$$Effect = E0 + (E_{max} \times Ce^N)/(EC_{50}^N + Ce^N)$$

Where $E0$ is the baseline response, E_{max} is the maximum effect change, Ce is the concentration in the effect compartment, EC_{50} is the concentration producing 50% E_{max} and N is the Hill coefficient defining the steepness of the concentration–response curve (Figure 1).

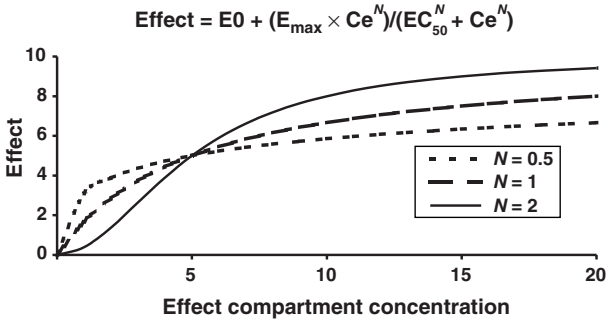

Figure 1
The Sigmoid E_{max} model. The steepness of the slope is determined by the Hill coefficient (N).

Observed effects may not be directly related to serum concentration. There may be a delay because of transfer of the drug to effect site (D-tubocurare at the neuromuscular junction), a lag-time (furosemide at the luminal surface of the renal tubule), physiological response (antipyretic action mediated through the hypothalamus), active metabolite (caffeine from theophylline in premature neonates) or synthesis of physiological substances (warfarin inhibition of vitamin K epoxidase). (55) The effect compartment concentration is not the same as the blood or serum concentration. A T_{eq} between serum or blood and effect compartment can be used to describe this time delay. By simultaneously solving PK and PD equations it is possible to estimate effect compartment concentrations.

Difficulties comparing drugs in children

Ethical issues

Review Boards and Ethics Committees view children differently than adults. It is not considered ethical to enrol children in trials solely for the good of future patients. Developmental issues, the inability to give informed consent (56), blood sampling requirements (57), and questions about payment for research participation (58) make paediatric research more difficult than adult. These issues have recently been reviewed in *Paediatric Anaesthesia* in a series of three reviews, examining the changes in the law in the last 10 years in relation to ethics and the practice of paediatric anaesthesia. These reviews cover, in a practical question and answer format, the topics of consent, research, intensive care and organ donation issues in children (59–61).

Type of pain

An outcome measure is vital to describe PD. However, acute pain is a complex sensation composed of elements beyond simple pathophysiology. Behavioural, cultural and psychological aspects contribute to its expression. It may vary between individuals depending on past experiences and duration. Early painful memories as a neonate may lead to abnormal behavioural patterns or altered sensory processing in later life (62). Visceral pain is quite different in nature from somatic pain. NSAIDs may better control visceral pain because of bladder spasm that is contributed by prostaglandin (63, 64). Similarly, NSAIDs may improve bone and joint pain better than paracetamol. Comparison of treatment modalities after different types of pain insults such as in children presenting for day-stay surgery may not be reasonable. The threshold at which pain requires management also varies between individuals. Gauthier *et al*. (65) have reported a pain treatment threshold of 5.3 units (VAS, 0–10) with a coefficient of variation of 30% after minor uncomplicated surgery in children.

Placebo effects

The placebo effect accounted for a mean pain reduction of 5.6 (VAS, 0–10) at 3 h in a recent study investigating paracetamol PD after tonsillectomy (66). The placebo response in that study reflected a combination of placebo effect, natural pain resolution, behavioural pain coping mechanisms and our inability to discriminate pain from emergence phenomena in the early postoperative period (67). Following emergence from anaesthesia, children were reunited with family, given access to video movies and allowed flavoured ice. These are all important contributors to the relief of pain that was described as the placebo response. Differentiating this placebo response from drug effect can be difficult. Ethical considerations often preclude a group of children randomized to receive a placebo drug. Korpela *et al*. (49) report that 10% of children given a placebo drug required no rescue morphine after day-stay surgery. The continuing use of placebo controls has been strongly argued against in the literature (68).

Pain and temperature fluctuations

Pathological states may resolve, worsen or remain static and the interpretation of the impact of medication on these changes can be complex (69). Neither pain nor temperature is constant over time. Pain waxes and wanes. Tonsillectomy pain, a model often used to investigate analgesic medication in children resolves over 2 weeks. Pain scores in children appear to decrease after only 3 days, but are often worse on the second or third day (70–72). Fever can be cyclical in nature or affected by environmental factors such

as swaddling, ambient temperature or radiant heat loss through a nearby window.

Age related pain scoring and comparisons between age groups

Children aged over 8 years can use visual-analogue pain scales. Between the ages of 3 and 8 years face scales or colour analogue scales are commonly used (73–75). Discordance between these two scales has been reported within this age band (76). Pain assessment may vary between caregivers, researchers and nurses (77). Behavioural observational scales are used in neonates, infants and children younger than 4 years. These may under represent the intensity of persistent pain (76). Physiological indexes of pain may be nonspecific. For example, hypovolaemia, hypoxia or drugs, rather than pain may cause tachycardia (78).

The assessment of pain at different ages involves different scoring systems with assessment values that may not be longitudinally comparable. Pain in neonates cannot be directly compared with that in older children. The pain sensitivity and response in a neonate may be different from an older child. Descending inhibitory pathways develop later than afferent excitatory pathways in the premature neonate (79). There is a lower threshold of the cutaneous flexion reflex (80, 81). Prolonged windup and hyperalgesia occurs following neonatal skin wounds and may be associated with excessive nerve sprouting because of nerve growth factor (82).

Drop outs

Patients who receive rescue medication and are withdrawn from a study may introduce additional bias as the remaining study patients are those who do not have such severe pain; the reason for their reduced analgesia may not be solely pharmaceutical (83).

PK covariates – age and size modelling

The per kilogram and surface area models may be inappropriate for scaling small children to adults (84). It is possible to show that in almost all species including humans, the log of basal metabolic rate (BMR) plotted against the log of body weight produces a straight line with a slope of 3/4. West *et al*. (85,86) have used fractal geometry to mathematically explain this phenomenon. A great many physiological, structural and time related variables scale predictably within and between species with weight exponents of 0.75, 1 and 0.25, respectively. These allometric '1/4 power' models can be applied to PK parameter estimates in children, e.g. clearance (0.75), half-life (0.25), volume of distribution (1). A dose ($mg \cdot kg^{-1}$) given to a 1-year-old child will have lower serum concentrations than the same dose ($mg \cdot kg^{-1}$) given to a 10-year-old child because clearance ($l \cdot kg^{-1} \cdot h^{-1}$) is greater in the younger child. Dose–response relationships will consequently change with age unless PK parameters are standardised for size.

The first few years of life are a time of growth and maturation of enzymatic processes. By choosing weight as the primary covariate, the secondary effects of age can be investigated. There are few biological models for the effect of age on clearance or apparent volume, but first order processes, which are common in biology, have been assumed (87). Covariates such as renal function, gender, concomitant drug therapy, illness can all be investigated and their effect quantified.

Chirality

Many NSAIDs exhibit stereoselectivity. Ketorolac, for example, is supplied and administered as a racemic mixture that contains a 1 : 1 ratio of the R(+) and S(−) stereoisomers. Pharmacological activity resides almost exclusively with the S(−) stereoisomer. Clearance of the S(−) enantiomer was four times that of the R(+) enantiomerin (6.2 vs. 1.4 $ml \cdot min^{-1}\ kg^{-1}$) in children 3–18 years (88). Terminal half-life of S(−)-ketorolac was 40% that of the R(+) enantiomer (107 vs. 259 min), and the apparent volume of distribution of the S(−) enantiomer was greater than that of the R(+) form (0.82 vs. 0.50 $l \cdot kg^{-1}$). Recovery of S(−)-ketorolac glucuronide was 2.3 times that of the R(+) enantiomer. Because of the greater clearance and shorter half-life of S(−)-ketorolac, pharmacokinetic predictions based on racemic assays may overestimate the duration of pharmacological effect. Enantiomeric pharmacokinetic differences may be explained by

stereoselective plasma protein binding and selective glucuronidation of the S(−) enantiomer (88).

PK and PD variability

Population PK parameter estimates are associated with considerable variability. Typical values of 50% for compliance with medication regimens, 30% for absorption, 10% for tissue distribution, 50% for metabolic elimination and 20% for renal elimination are reported (89). These parameter variabilities contribute to the large concentration range seen after a rectal paracetamol dosing (Figure 2) (90). An extreme example of clearance variability is demonstrated by codeine. The *O*-methylation (cytochrome P450 enzyme CYP2D6) of codeine to morphine is lacking in 7% of Caucasians (91, 92); contributing to the observed NNT 95% CI for dihydrocodeine 30 mg of 4.5 to >10000 (53). The use of concentration to link dose and effect allows PK variability to be separated from PD variability. The reduction in total variability produced by the removal of the PK component has been estimated to be 50% or greater.

Pharmacodynamic (concentration–effect) variability also exists. The contribution of variability because of distribution from the blood to the site of action will depend largely on changes in perfusion of target tissue (5–50%) and efficacy variability (30%) also exist. The observed response may not be a direct consequence of drug–receptor binding, but rather through intermediate physiological mechanisms (e.g. antipyretics, angiotensin converting enzyme inhibitors). A typical value for this variability is 30% (89).

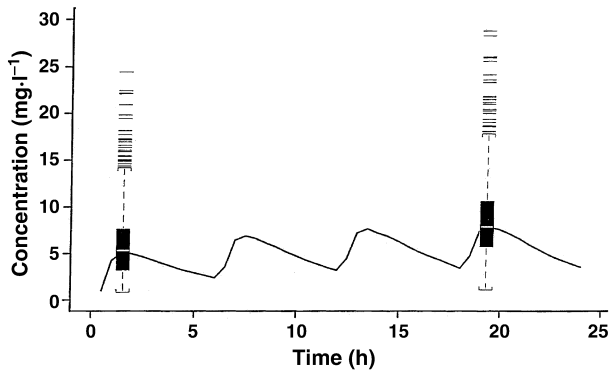

Figure 2
Median paracetamol concentrations after 12.5 mg·kg^{-1} 6 h given rectally. Variability is demonstrated for the maximum concentrations after the first and fourth doses using box and whisker plots. The solid box represents the 50th centile. Values outside the 97.5% centile are shown individually. From Anderson *et al*. (90).

Many clinical studies in which paracetamol is compared with another analgesic are destined either to fail to show a difference between the two analgesic treatments or to have inadequate power because pain score reporting methods, the pain stimulus and PK and PD parameters all have large variability.

Population modelling methods

The method used to estimate population parameters might also have an impact on results. Three methods are commonly used – the naïve pooled data, the standard two-stage and the 'true' population approaches.

The naïve pooled data approach may be satisfactory if data are extensive for each individual and there is only minor inter-individual variability, but may result in misrepresentation if data are few (93). It is possible to 'wash out' any observed effect. For example, if a population is randomized to receive either drug A or drug B and serum drug concentrations and pain scores after a surgical insult measured, then no difference in effect may be noted. Both drugs will result in some patients with high concentrations and good effect and some with low concentrations and poor effect. However, the naïve-pooled results will wash out these dose–concentration and concentration–effect responses. Mean data may reflect no difference in the two populations.

The standard two-stage approach ignores the imprecision in the estimate of an individual's structural parameter. Further, if the estimates are not based on a similar number of measurements for each individual, or if the response in one individual is much more variable than another, some form of weighting is required.

Population modelling using mixed effect models (e.g. NONMEM), in which differences in parameters between subjects are modelled using distributions for these parameters, are superior. Explanatory covariates can also be introduced that explain part of the inter-individual variability. Interpretation of truncated individual data or missing data is also possible with this type of analysis (94,95).

Sigmoid E_{max} models for antipyresis and analgesia

Antipyresis

There are few studies describing the PD of a NSAID and paracetamol using the same population and study design. Ibuprofen is the most common NSAID antipyretic studied (7–10). Kelley *et al*. (9) studied children ($n = 39$; age range, 11 months to 11.5 years) randomly selected to receive a single dose of either 6 mg·kg^{-1} of liquid ibuprofen or 10–15 mg·kg^{-1} of liquid paracetamol (mean dose given, 11.6 SD 0.7). Temperature reduction for the ibuprofen dose was significantly different than that of the paracetamol dose at later time points. Naïve pooled data from Kelley *et al*. (9) have been modelled using a first order absorption, first order elimination PK model with delayed effects accounted for by an effect compartment model using MKMODEL (96,97). Effect compartment time–concentration relationships are shown in Figures 3a (paracetamol) and 4a (ibuprofen). Pharmacodynamic parameter estimates are shown in Table 2. The effect compartment concentration–response relationship is shown in Figures 3b (paracetamol) and 4b (ibuprofen). The maximal response cannot be estimated with any certainty because higher doses were not explored, although an E_{max} of 5.4°F (3°C) would be clinically reasonable. Several studies have shown fever reductions of up to 3°F after either paracetamol (10–12.5 mg·kg^{-1}) or ibuprofen (5–10 mg·kg^{-1}) (39, 40, 98). Importantly, the shapes of the two curves are quite different. The paracetamol curve is initially concave upward while ibuprofen has an almost

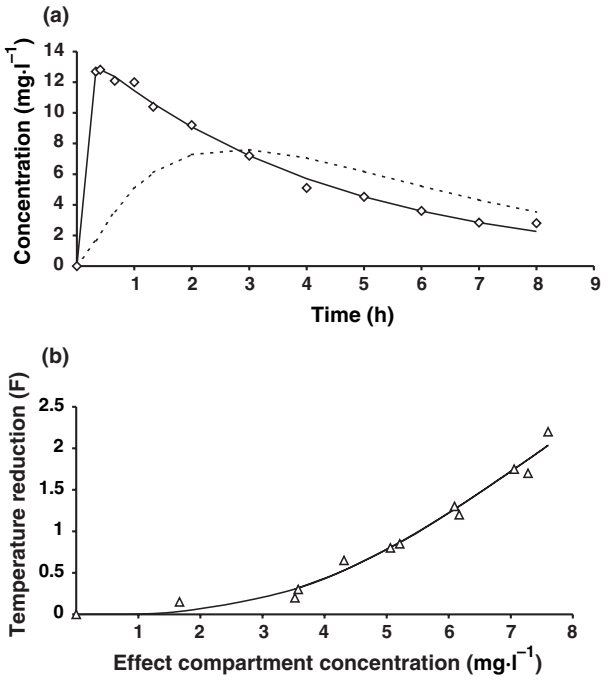

Figure 3
(a) Effect compartment concentrations (dotted line) and their relationship to paracetamol serum concentrations (bold line). (b) effect compartment concentration–response relationship for paracetamol. antipyresis Data from Kelley *et al*. (9).

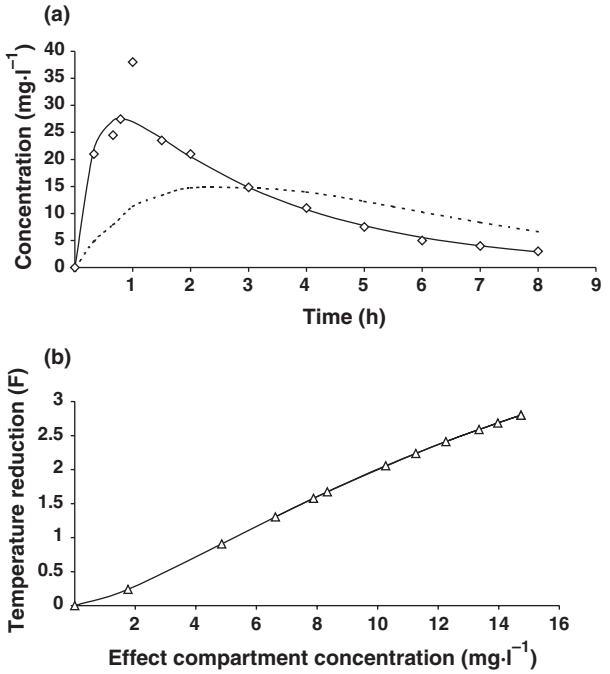

Figure 4
(a) Effect compartment concentrations (dotted line) and their relationship to paracetamol serum concentrations (bold line). (b) Effect compartment concentration–response relationship for paracetamol. antipyresis Data from Kelley *et al*. (9).

Table 2
Antipyresis pharmacodynamic parameter estimates [data from Kelley *et al*. (9)]

Parameter	*Paracetamol*	*Ibuprofen*
E_{max}	5.4°F	5.4°F
EC_{50}	9.7 mg·l^{-1}	16 mg·l^{-1}
N	2.9	1.43
T_{eq}	1.2 h	1.6 h

E_{max} = maximum pain reduction because of antipyretic drug, EC_{50} = concentration producing 50% E_{max}, N = Hill coefficient, T_{eq} = effect compartment equilibration half-time.

linear relationship. Consequently at lower concentrations ibuprofen will generate a greater response than paracetamol. In order to compare the efficacy of these two antipyretic drugs we require response data at higher concentrations than those currently reported do. The dose given and where the subsequent effect compartment concentration lies on the response curve will influence observed effect.

Interpretation of antipyretic data is more complicated than the above analysis of data from Kelley *et al*. (9) suggests. Brown *et al*. (7) have reported a linked population PK–PD model for antipyresis using mixed effects models. The addition of a slope and/or a sinusoidal cyclic function to the Sigmoid E_{max} component was required to fit the PD data satisfactorily. The initial temperature also influenced the antipyretic effect.

The interpretation of the concentration–response relationship is confounded by the disease process, initial temperature, dosing regimens and fever fluctuation ensuring that direct comparison between paracetamol and ibuprofen is difficult. A large number of studies have suggested that the clinical effectiveness of these two drugs is similar. No clinical trials have been conducted that demonstrate superior effect when both drugs are used compared with one alone.

Analgesia

Similar considerations apply to analgesic models. Pain fluctuations, pain type and placebo effects complicate interpretation. NSAID concentration–response relationships have been described in adults (99–104). Mandema *et al*. (99) studied patients ($n = 522$) given a single oral or intramuscular administration of placebo or a single intramuscular dose of 10, 30, 60, or 90 mg ketorolac for postoperative pain relief after orthopaedic surgery. Mixed effects models were used. Pain relief was found to be a function of drug concentration (E_{max} model), time (waxing and waning of placebo effect), and an individual random effect. The EC_{50} and T_{eq} were 0.37 mg·l^{-1} and 24 min (Table 3). Only 25% of the patients achieved adequate pain relief with placebo. The concentration–response relationship is shown in Figure 5.

Anderson *et al*. (66) investigated paracetamol PD using mixed effects modelling after tonsillectomy in 182 children aged 9.0 (SD 3.0) years and weight 37.9 (SD 16.6) kg. Placebo effects and drug effects were modelled by effect site concentration models. A one-compartment model with first order input, lag time and first order elimination was used to describe the population PK of paracetamol, standardized for size with allometric models. PD population parameter estimates (population variability CV) for an E_{max} model, in which the greatest possible pain relief (VAS 0–10) equates to an E_{max} of 10, were E_{max} 5.17 (64%) and EC_{50} 9.98 (107%) mg·l^{-1} (Table 3, Figure 6). The T_{eq} of the analgesic effect compartment was 53 (217%) min. A target concentration of 10 mg·l^{-1} was suggested for tonsillectomy pain (66).

Any comparison between paracetamol and ketorolac using these data is difficult. Ketorolac was studied in adults after orthopaedic surgery, paracetamol in children after tonsillectomy. The T_{eq} of ketorolac appears shorter than paracetamol (24 vs.

Table 3
Analgesia pharmacodynamic parameter estimates from Anderson *et al*. (66) and Mandema *et al*. (99)

Parameter	*Paracetamol*	*Ketorolac*
E_{max}	5.17 pain units	8.5 pain units
E0	10 fixed	10 fixed
EC_{50}	9.98 mg·l^{-1}	0.37 mg·l^{-1}
N	1	1
T_{eq}	53 min	24 min

E_{max} = maximum pain reduction because of analgesic drug, E_0 = baseline response (fixed at 10, maximal pain), EC_{50} = concconcentration producing 50% E_{max}, N = Hill coefficient, T_{eq} = effect compartment equilibration half-time.

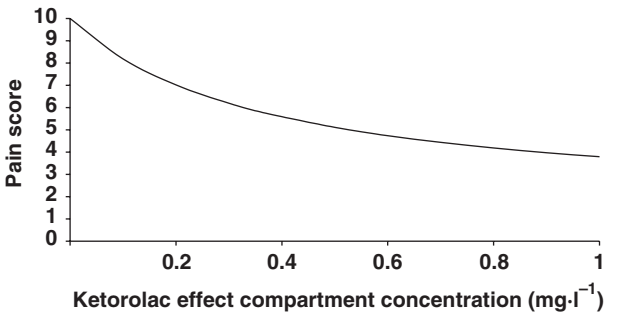

Figure 5
Effect compartment concentration–analgesic response relationship for ketorolac in adults after orthopaedic surgery. A 5 category ordinal scale (VAS) was used to measure effectiveness – this scale has been transformed to a VAS 0–10 scale in order to compare with paracetamol. Data from Mandema *et al*. (99).

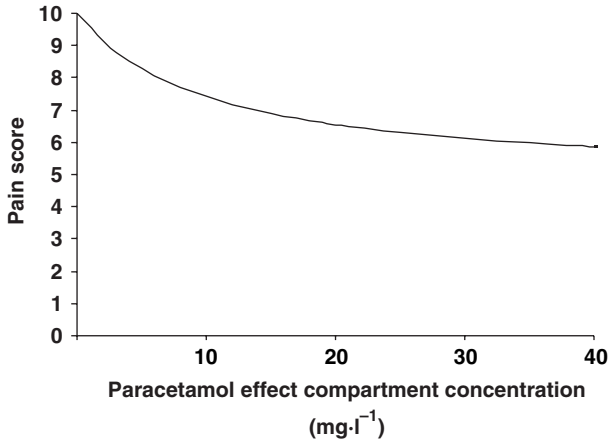

Figure 6
Effect compartment concentration–analgesic response relationship for paracetamol in children after tonsillectomy. A VAS pain score (0–10) measured effectiveness. Data from Anderson *et al*. (66).

53 min), suggesting earlier effect. Ketorolac also appears to have greater efficacy. However, there are no studies comparing concentration–response curves for a NSAID and paracetamol in children after the same pain insult. Our knowledge remains limited.

Safety issues

Paracetamol

The maximum dose possible is dictated not by PK–PD considerations, but by concerns about paracetamol induced hepatotoxicity.

Chronic use of paracetamol

There has been a reticence among practitioners to prescribe doses of paracetamol greater than 90 $mg \cdot kg^{-1} \cdot day^{-1}$ (105). Paracetamol overdose results in increased production of highly reactive electrophilic arylating metabolites by the hepatic cytochrome P-450-dependent mixed function oxidase enzyme system (CYP2E1). (106) The toxic metabolite of paracetamol, *N*-acetyl-*p*-benzoquinone imine (NAPQI) (107), binds to intracellular hepatic macromolecules to produce cell necrosis and damage. Paracetamol concentrations may rise in paediatric patients with low clearance after regular doses of 15 $mg \cdot kg^{-1}$ 4 h (108). There is adult evidence of glutathione depletion in adult volunteers given doses of 0.5 and 3 g paracetamol separated by 4–10 days (109). Significant hepatic and renal disease, malnutrition and dehydration increase the propensity for toxicity. Medications that induce the hepatic P450 CYP2E1, 1A2 and 3A4 systems (e.g. phenobarbitone, phenytoin, and rifampicin) may also increase the risk of hepatotoxicity. It is currently impossible to predict which individuals have an enhanced susceptibility to cellular injury from paracetamol. The coingestion of therapeutic drugs, foodstuffs or other xenobiotics has potential to induce these enzymes (110).

The influence of disease on paracetamol toxicity is unknown. It has been speculated that ingestion of paracetamol increases the potential for liver injury by another cause, such as a viral agent (111). More recently, hepatotoxicity causing death or requiring liver transplantation has been reported with doses above 75 $mg \cdot kg^{-1} \cdot day^{-1}$ in children and 90 $mg \cdot kg^{-1} \cdot day^{-1}$ in infants (110, 112–114). It is possible that even these regimens may cause hepatotoxicity if used for longer than 2–3 days (110). These reports (110,112–114) and others from Australia (115,116) and Scotland (117) are concerning. Kozer *et al*. (118) have demonstrated that ill children receiving repeated large doses of paracetamol (>90 $mg \cdot kg^{-1} \cdot day^{-1}$) may show abnormalities in liver function. It is unknown if there is a difference in the propensity to toxicity between those given paracetamol for fever and those given paracetamol for postoperative analgesia.

Single dose of paracetamol

The plasma concentration associated with toxicity after a single dose of paracetamol in children is extrapolated from adult data. The Rumack–Matthew (119) paracetamol toxicity nomogram is widely used to guide management of paracetamol overdose in adults and children. This nomogram was derived from a study by Prescott *et al*. (120) of 30 adult patients who ingested an overdose of paracetamol. In poisoned patients with similar initial concentrations, the half-life in those without liver damage was 2.9 (S.E. 0.3) h and in those with liver damage 7.6 (S.E. 0.8) h. Paracetamol concentrations of more than 300 $mg \cdot l^{-1}$ at 4 h were always associated with severe hepatic lesions, but none was observed in patients with concentrations less than 150 $mg \cdot l^{-1}$. The

half-life was less than 4 h in all patients without liver damage.

Clearance is a nonlinear function of weight, while volume is a linear function of weight. Dose is usually expressed as a linear function of weight. The 4-h concentration is determined by clearance, not volume in children, because absorption is rapid after oral elixir. As a consequence younger children (1–6 years) require larger doses (225 $mg \cdot kg^{-1}$) than older children and adults (150 $mg \cdot kg^{-1}$) to achieve similar concentrations at 4 h (121,122). This has been demonstrated in animals. Young rats have a higher median lethal dose than older rats (123). More drug is required to produce a hepatotoxic reaction (123).

Young children under the age of 6 years are thought to be less susceptible to toxicity than older children and adults (119). Less than 5% of children below 6 years with paracetamol concentrations above the Rumack–Matthew treatment line will develop transient hepatic abnormalities (124). This may, in part, be attributable to the shorter half-life seen in children. In addition, young rats have been reported to have an increase in the rate of glutathione synthesis compared with older rats, as well as a capacity to increase glutathione levels after depletion (125). Glutathione may then provide increased detoxification.

Neonates can produce hepatotoxic metabolites (e.g. NAPQI), but there are suggestions of a lower activity of cytochrome P-450 in neonates. This may explain the low occurrence of paracetamol-induced hepatotoxicity seen in neonates (126,127), despite reports of high serum concentrations (75, 360 $mg \cdot l^{-1}$) in new-born neonates (126,128). Placental transfer from the mother achieved these concentrations.

NSAIDs

The NSAIDs have potential to cause GI irritation, blood clotting disorders, renal impairment and bronchoconstriction (129,130) – effects postulated to be related to COX-1/COX-2 ratios, although this concept may be an oversimplification (131, 132). For example, the COX-2 inhibitors rofecoxib and celecoxib produce qualitative changes in urinary prostaglandin excretion, glomerular filtration rate, sodium retention, and their consequences similar to nonselective NSAIDs. COX-2 is constitutively expressed in renal tissues of all species. It seems unlikely that these COX-2 inhibitors will offer renal safety benefits over nonselective NSAID therapies. It is reasonable to assume that all NSAIDs, including COX-2-selective inhibitors, share a similar risk for adverse renal effects (133).

Renal effects

The effect of short-term treatment with NSAIDs on healthy kidneys is negligible. Large studies involving ibuprofen (134–136) and ketorolac (137) have shown little risk. Similar data are reported in children suffering juvenile rheumatoid arthritis (JIA) given NSAIDs as long-term treatment (138,139). However, renal compromise is described in children compromised by dehydration, hypovolaemia, hypotension or preexisting renal disease (140–145). NSAIDs may also potentiate the toxicity of other drugs such as aminoglycosides and cyclosporin (146,147).

Gastrointestinal effects

Adverse GI effects are significant in adults, particularly in those with peptic ulcer disease, *H. pylori* or advanced age (148–150). The risk of acute GI bleeding in children given short-term ibuprofen was estimated to be 7.2/100 000 (CI 2-18/100 000) (134, 136) and was not different from those children given paracetamol. Similar data are reported in children given ketorolac for acute pain (144). The incidence of clinically significant gastropathy is comparable with adults in children given NSAIDs for JIA (151,152), but gastro-duodenal injury may be very much higher (75%) depending on assessment criteria (e.g. abdominal pain, anaemia, endoscopy) (153).

Bleeding propensity

The commonly used NSAIDs such as ketorolac, diclofenac, ibuprofen and ketoprofen have reversible antiplatelet effects, which are attributable to the inhibition of thromboxane synthesis. This side effect is of concern during the perioperative period (154,155). Bleeding time is usually slightly increased, but in most patients it remains within normal limits in children with normal coagulation systems (156–158). There is conflicting evidence of the potential for increased surgical-site bleeding after tonsillectomy but, for other types of paediatric surgery, numerous clinical studies have confirmed that the NSAIDs are not associated with increased bleeding (46,159–161).

Studies involving the use of ketorolac analgesia for tonsillectomy have fuelled the debate against NSAID use in the perioperative period for this procedure. Several prospective (155,162) and retrospective studies (26,163,164) reported increased bleeding in children given approximately 1 $mg \cdot kg^{-1}$ ketorolac *iv* preoperatively or intraoperatively. Other authors were unable to demonstrate increased bleeding after tonsillectomy (165–167). The increased bleeding may be attributable to the dose used and whether it is given preoperatively or postoperatively. Strom *et al.* (167) reported a dose–response relationship for this bleeding propensity.

Forrest *et al.* subsequently recommended an intravenous dose of ketorolac in children of 0.5 $mg \cdot kg^{-1}$, followed either by bolus injections of 1.0 $mg \cdot kg^{-1}$ 6 h or an intravenous infusion of 0.17 $mg \cdot kg^{-1} \cdot h^{-1}$. The maximum daily dosage is 90 mg, and the maximum duration of treatment is 48 h. An oral dose of 0.25 $mg \cdot kg^{-1}$ to a maximum of 1.0 $mg \cdot kg^{-1} \cdot day^{-1}$, with a maximum duration of 7 days was suggested. As with paracetamol, older children may require somewhat lower dosages, while infants and young children may require slightly higher dosages (effect of size models on PK) to achieve the same level of pain relief, although a target concentration is undefined. Ketorolac is not recommended for use for infants aged less than 1 year (144).

The arguments against alternative NSAID use during tonsillectomy are not as strong as those against ketorolac. Ketoprofen doses 0.3–3 $mg \cdot kg^{-1}$ have been used (168,169) with varying effects on bleeding (168–170). Ketoprofen is not recommended in many countries because of insufficient efficacy and tolerability data. Diclofenac (38,46,171–173) and ibuprofen (42,174,175) appear to have, on balance, favourable profiles. Propensity to bleeding is reduced compared with ketorolac, but no therapeutic target concentrations for diclofenac (23) or ibuprofen have been defined.

Conclusions

NSAID and paracetamol doses are often compared without the PD and PK knowledge needed to support them. Pharmacodynamic models are needed to compare drugs and to predict the target concentration for a given target effect (176). We need to define what target effect and consequent target concentration is required in different pain circumstances for the different drugs. The dose needed to achieve the target concentration can then be predicted from PK (and covariate) information (177). Safety issues may limit the target concentration possible, as with paracetamol and ketorolac. Efficacy of the two drugs may be similar, but concerns about side effects may limit dose and consequent clinical effect achievable.

In recent years, paracetamol PK and PD in children have been reexamined. Much work remains undone, particularly for neonatal pain (178). A pharmacodynamic model for postoperative tonsillectomy pain has been suggested (66), but other types of pain stimuli or age-related differences have not been examined. Despite the introduction of the specific COX-2 inhibitor NSAIDs (132,179,180), large holes remain in our PK–PD understanding of commonly used NSAIDs in children. Efficacy may vary with age or pain type. Target concentrations are undefined. Limited data exist concerning PK or age-related changes for commonly used NSAIDs. Dose is often defined by toxicity data that may effect subpopulations only. The reason why some children suffer toxicity while others are unaffected is unknown, even for paracetamol. Concentration–response curves are wanting for these common analgesic drugs and without these PD data it remains difficult to directly compare the effectiveness of the NSAIDs to paracetamol.

Acknowledgement

This study was supported solely from institutional and/or departmental sources.

References

1 Oermann CM, Sockrider MM, Konstan MW. The use of anti-inflammatory medications in cystic fibrosis: trends and physician attitudes. *Chest* 1999; **115:** 1053–1058.
2 Konstan MW, Byard PJ, Hoppel CL *et al.* Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med* 1995; **332:** 848–854.
3 Konstan MW, Hoppel CL, Chai BL *et al.* Ibuprofen in children with cystic fibrosis: pharmacokinetics and adverse effects. *J Pediatr* 1991; **118:** 956–964.
4 Scott CS, Retsch-Bogart GZ, Kustra RP *et al.* The pharmacokinetics of ibuprofen suspension, chewable tablets, and tablets in children with cystic fibrosis. *J Pediatr* 1999; **134:** 58–63.

5 Van Overmeire B, Smets K, Lecoutere D *et al.* A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med* 2000; **343:** 674–681.
6 Litalien C, Jacqz-Aigrain E. Risks and benefits of nonsteroidal anti-inflammatory drugs in children: a comparison with paracetamol. *Paediatr Drugs* 2001; **3:** 817–858.
7 Brown RD, Kearns GL, Wilson JT. Integrated pharmacokinetic-pharmacodynamic model for acetaminophen, ibuprofen, and placebo antipyresis in children. *J Pharmacokinet Biopharm* 1998; **26:** 559–579.
8 Kauffman RE, Nelson MV. Effect of age on ibuprofen pharmacokinetics and antipyretic response. *J Pediatr* 1992; **121:** 969–973.
9 Kelley MT, Walson PD, Edge JH *et al.* Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. *Clin Pharmacol Ther* 1992; **52:** 181–189.
10 Troconiz IF, Armenteros S, Planelles MV *et al.* Pharmacokinetic-pharmacodynamic modelling of the antipyretic effect of two oral formulations of ibuprofen. *Clin Pharmacokinet* 2000; **38:** 505–518.
11 Shaffer CL, Gal P, Ransom JL *et al.* Effect of age and birth weight on indomethacin pharmacodynamics in neonates treated for patent ductus arteriosus. *Crit Care Med* 2002; **30:** 343–348.
12 Mitchell JA, Akarasereenont P, Thiemermann C *et al.* Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci U S A* 1993; **90:** 11693–11697.
13 Piletta P, Porchet HC, Dayer P. Central analgesic effect of acetaminophen but not of aspirin. *Clin Pharmacol Ther* 1991; **49:** 350–354.
14 Bjorkman R, Hallman KM, Hedner J *et al.* Acetaminophen blocks spinal hyperalgesia induced by NMDA and substance P. *Pain* 1994; **57:** 259–264.
15 Bjorkman R. Central antinociceptive effects of non-steroidal anti-inflammatory drugs and paracetamol. Experimental studies in the rat. *Acta Anaesthesiol Scand Suppl* 1995; **103:** 1–44.
16 Bourne HR. Drug receptors & pharmacodynamics. In: Katzung BG, ed. *Basic & Clinical Pharmacology*. Stamford: Appleton & Lange, 1998: 28.
17 Sheiner L, Tozer T. Clinical pharmacokinetics: The use of plasma concentrations of drugs. In: Melmon K, Morelli H, eds. *Clinical Pharmacology: Basic Principles of Therapeutics*. New York: Macmillan, 1978: 71–109.
18 Beringer P, Aminimanizani A, Synold T *et al.* Development of population pharmacokinetic models and optimal sampling times for ibuprofen tablet and suspension formulations in children with cystic fibrosis. *Ther Drug Monit* 2002; **24:** 315–321.
19 Splinter WM, Reid CW, Roberts DJ *et al.* Reducing pain after inguinal hernia repair in children: caudal anesthesia versus ketorolac tromethamine. *Anesthesiology* 1997; **87:** 542–546.
20 Ryhanen P, Adamski J, Puhakka K *et al.* Postoperative pain relief in children. A comparison between caudal bupivacaine and intramuscular diclofenac sodium. *Anaesthesia* 1994; **49:** 57–61.
21 Moores MA, Wandless JG, Fell D. Paediatric postoperative analgesia. A comparison of rectal diclofenac with caudal bupivacaine after inguinal herniotomy. *Anaesthesia* 1990; **45:** 156–158.
22 Rolf C, Engstrom B, Beauchard C *et al.* Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy. *Rheumatology (Oxford)* 1999; **38:** 564–567.
23 Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac. Therapeutic insights and pitfalls. *Clin Pharmacokinet* 1997; **33:** 184–213.
24 Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 2 – Clinical use. *Paediatr Anaesth* 1997; **7:** 93–101.
25 Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 1 – Pharmacokinetics. *Paediatr Anaesth* 1997; **7:** 5–11.
26 Gunter JB, Varughese AM, Harrington JF *et al.* Recovery and complications after tonsillectomy in children: a comparison of ketorolac and morphine. *Anesth Analg* 1995; **81:** 1136–1141.
27 Munro HM, Riegger LQ, Reynolds PI *et al.* Comparison of the analgesic and emetic properties of ketorolac and morphine for paediatric outpatient strabismus surgery. *Br J Anaesth* 1994; **72:** 624–628.
28 Inturrisi CE, Colburn WA. Application of pharmacokinetic-pharmacodynamic modeling to analgesia. In: Foley KM, Inturrisi CE, eds. *Advances in Pain Research and Therapy. Opioid Analgesics in the Management of Clinical Pain*. New York: Raven Press, 1986: 441–452.
29 Dahlstrom B, Bolme P, Feychting H *et al.* Morphine kinetics in children. *Clin Pharmacol Ther* 1979; **26:** 354–365.
30 Maunuksela EL, Kokki H, Bullingham RE. Comparison of intravenous ketorolac with morphine for postoperative pain in children. *Clin Pharmacol Ther* 1992; **52:** 436–443.
31 Maunuksela E-L, Olkkola KT. Nonsteroidal anti-inflammatory drugs in pediatric pain management. In: Schechter NL, Berde CB, Yaster M, eds. *Pain in Infants, Children, and Adolescents*. Philadelphia: Lippincott Williams & Wilkins, 2003: 171–80.
32 Watcha MF, Ramirez Ruiz M, White PF *et al.* Perioperative effects of oral ketorolac and acetaminophen in children undergoing bilateral myringotomy. *Can J Anaesth* 1992; **39:** 649–654.
33 Baer GA, Rorarius MG, Kolehmainen S *et al.* The effect of paracetamol or diclofenac administered before operation on postoperative pain and behaviour after adenoidectomy in small children. *Anaesthesia* 1992; **47:** 1078–1080.
34 Bennie RE, Boehringer LA, McMahon S *et al.* Postoperative analgesia with preoperative oral ibuprofen or acetaminophen in children undergoing myringotomy. *Paediatr Anaesth* 1997; **7:** 399–403.
35 Bertin L, Pons G, d'Athis P *et al.* A randomized, double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children. *Fundam Clin Pharmacol* 1996; **10:** 387–392.
36 Figueras Nadal C, Garcia de Miguel MJ, Gomez Campdera A *et al.* Effectiveness and tolerability of ibuprofen-arginine versus paracetamol in children with fever of likely infectious origin. *Acta Paediatr* 2002; **91:** 383–390.
37 Purssell E. Treating fever in children: paracetamol or ibuprofen? *Br J Community Nurs* 2002; **7:** 316–320.
38 Tawalbeh MI, Nawasreh OO, Husban AM. Comparative study of diclofenac sodium and paracetamol for treatment of pain after adenotonsillectomy in children. *Saudi Med J* 2001; **22:** 121–123.

39 Van Esch A, Van Steensel Moll HA, Steyerberg EW *et al.* Antipyretic efficacy of ibuprofen and acetaminophen in children with febrile seizures. *Arch Pediatr Adolesc Med* 1995; **149:** 632–637.

40 Walson PD, Galletta G, Braden NJ *et al.* Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther* 1989; **46:** 9–17.

41 Goyal PK, Chandra J, Unnikrishnan G *et al.* Double blind randomized comparative evaluation of nimesulide and paracetamol as antipyretics. *Indian Pediatr* 1998; **35:** 519–522.

42 Pickering AE, Bridge HS, Nolan J *et al.* Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children. *Br J Anaesth* 2002; **88:** 72–77.

43 Johnson GH, Van Wagoner JD, Brown J *et al.* Bromfenac sodium, acetaminophen/oxycodone, ibuprofen, and placebo for relief of postoperative pain. *Clin Ther* 1997; **19:** 507–519.

44 Romsing J, Ostergaard D, Senderovitz T *et al.* Pharmacokinetics of oral diclofenac and acetaminophen in children after surgery. *Paediatr Anaesth* 2001; **11:** 205–213.

45 Anderson BJ, Holford NHG. Rectal paracetamol dosing regimens: determination by computer simulation. *Paediatr Anaesth* 1997; **7:** 451–455.

46 Morton NS, O'Brien K. Analgesic efficacy of paracetamol and diclofenac in children receiving PCA morphine. *Br J Anaesth* 1999; **82:** 715–717.

47 Vetter TR, Heiner EJ. Intravenous ketorolac as an adjuvant to pediatric patient-controlled analgesia with morphine. *J Clin Anesth* 1994; **6:** 110–113.

48 Oztekin S, Hepaguslar H, Kar AA *et al.* Preemptive diclofenac reduces morphine use after remifentanil-based anaesthesia for tonsillectomy. *Paediatr Anaesth* 2002; **12:** 694–699.

49 Korpela R, Korvenoja P, Meretoja OA. Morphine-sparing effect of acetaminophen in pediatric day-case surgery. *Anesthesiology* 1999; **91:** 442–447.

50 Moore A, Moore O, McQuay H *et al.* Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: use of pain intensity and visual analogue scales. *Pain* 1997; **69:** 311–315.

51 Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: verification from independent data. *Pain* 1997; **69:** 127–130.

52 Moore A, Collins S, Carroll D *et al.* Single dose paracetamol (acetaminophen), with and without codeine, for postoperative pain. *Cochrane Database Syst Rev* 2000; 2.

53 Collins SL, Moore RA, McQuay HJ *et al.* Single dose oral ibuprofen and diclofenac for postoperative pain. *Cochrane Database Syst Rev* 2002.

54 Prescott LF. Gastrointestinal absorption of drugs. *Med Clin North Am* 1974; **58:** 907–916.

55 Holford NHG. Parametric models of the time course of drug action. In: Van Boxtel CJ, Holford NHG, Danhof M, eds. *The In Vivo Study of Drug Action*. Amsterdam: Elsevier, 1992: 61–69.

56 Randolph AG, Lacroix J. Randomized clinical trials in pediatric critical care: rarely done but desparately need. *Pediatr Crit Care Med* 2002; **3:** 102–106.

57 Oliveira EJ, Watson DG, Morton NS. A simple microanalytical technique for the determination of paracetamol and its main metabolites in blood spots. *J Pharm Biomed Anal* 2002; **29:** 803–809.

58 Fernhoff PM. Paying for children to participate in research: a slippery slope or an enlightened stairway? *J Pediatr* 2002; **141:** 153–154.

59 Edgar J, Morton NS, Pace NA. Review of ethics in paediatric anaesthesia: intensive care issues. *Paediatr Anaesth* 2001; **11:** 597–601.

60 Edgar J, Morton NS, Pace NA. Review of ethics in paediatric anaesthesia: research issues. *Paediatr Anaesth* 2001; **11:** 473–477.

61 Edgar J, Morton NS, Pace NA. Review of ethics in paediatric anaesthesia: consent issues. *Paediatr Anaesth* 2001; **11:** 355–359.

62 Porter FL, Grunau RE, Anand KJ. Long-term effects of pain in infants. *J Dev Behav Pediatr* 1999; **20:** 253–261.

63 Chauhan RD, Idom CB, Noe HN. Safety of ketorolac in the pediatric population after ureteroneocystostomy. *J Urol* 2001; **166:** 1873–1875.

64 Park JM, Houck CS, Sethna NF *et al.* Ketorolac suppresses postoperative bladder spasms after pediatric ureteral reimplantation. *Anesth Analg* 2000; **91:** 11–15.

65 Gauthier JC, Finley GA, McGrath PJ. Children's self-report of postoperative pain intensity and treatment threshold: determining the adequacy of medication. *Clin J Pain* 1998; **14:** 116–120.

66 Anderson BJ, Woollard GA, Holford NHG. Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy. *Eur J Clin Pharmacol* 2001; **57:** 559–569.

67 Johr M. Postanaesthesia excitation. *Paediatr Anaesth* 2002; **12:** 308–312.

68 Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med* 1994; **331:** 394–398.

69 Chan PL, Holford NH. Drug treatment effects on disease progression. *Annu Rev Pharmacol Toxicol* 2001; **41:** 625–659.

70 Lavy JA. Post-tonsillectomy pain: the difference between younger and older patients. *Int J Pediatr Otorhinolaryngol* 1997; **42:** 11–15.

71 Murthy P, Laing MR. Dissection tonsillectomy: pattern of post-operative pain, medication and resumption of normal activity. *J Laryngol Otol* 1998; **112:** 41–44.

72 Toma AG, Blanshard J, Eynon Lewis N *et al.* Post-tonsillectomy pain: the first ten days. *J Laryngol Otol* 1995; **109:** 963–964.

73 Beyer JE, Denyes MJ, Villarruel AM. The creation, validation, and continuing development of the Oucher: a measure of pain intensity in children. *J Pediatr Nurs* 1992; **7:** 335–346.

74 Bieri D, Reeve RA, Champion GD *et al.* The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: development, initial validation, and preliminary investigation for ratio scale properties. *Pain* 1990; **41:** 139–1350.

75 Chambers CT, Giesbrecht K, Craig KD *et al.* A comparison of faces scales for the measurement of pediatric pain: children's and parents' ratings. *Pain* 1999; **83:** 25–35.

76 Beyer JE, McGrath PJ, Berde CB. Discordance between self-report and behavioral pain measures in children aged 3–7 years after surgery. *J Pain Symptom Manage* 1990; **5:** 350–356.

77 Breau LM, Finley GA, McGrath PJ *et al.* Validation of the non-communicating children's pain checklist-postoperative version. *Anesthesiology* 2002; **96:** 528–535.

78 Berde CB, Sethna NF. Analgesics for the treatment of pain in children. *N Engl J Med* 2002; **347:** 1094–1103.

79 Fitzgerald M, Koltzenburg M. The functional development of descending inhibitory pathways in the dorsolateral funiculus of the newborn rat spinal cord. *Brain Res* 1986; **389:** 261–270.
80 Andrews K, Fitzgerald M. The cutaneous withdrawal reflex in human neonates: sensitization, receptive fields, and the effects of contralateral stimulation. *Pain* 1994; **56:** 95–101.
81 Andrews K, Fitzgerald M. Cutaneous flexion reflex in human neonates: a quantitative study of threshold and stimulus-response characteristics after single and repeated stimuli. *Dev Med Child Neurol* 1999; **41:** 696–703.
82 Fitzgerald M, Millard C, MacIntosh N. Hyperalgesia in premature infants. *Lancet* 1988; **1:** 292.
83 Sheiner LB. A new approach to the analysis of analgesic drug trials, illustrated with bromfenac data. *Clin Pharmacol Ther* 1994; **56:** 309–322.
84 Anderson BJ, Meakin GH. Scaling for size: some implications for paediatric anaesthesia dosing. *Paediatr Anaesth* 2002; **12:** 205–219.
85 West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. *Science* 1997; **276:** 122–126.
86 West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. *Science* 1999; **284:** 1677–1679.
87 Anderson BJ, van Lingen RA, Hansen TG *et al.* Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. *Anesthesiology* 2002; **96:** 1336–1345.
88 Kauffman RE, Lieh-Lai MW, Uy HG *et al.* Enantiomer-selective pharmacokinetics and metabolism of ketorolac in children. *Clin Pharmacol Ther* 1999; **65:** 382–388.
89 Holford NHG, Peck CC. Population pharmacodynamics and drug development. In: Van Boxtel CJ, Holford NHG, Danhof M, eds. *The In Vivo Study of Drug Action*. Amsterdam: Elsevier, 1992.
90 Anderson BJ, Monteleone J, Holford NHG. Variability of concentrations after rectal paracetamol. *Paediatr Anaesth* 1998; **8:** 274.
91 Williams DG, Hatch DJ, Howard RF. Codeine phosphate in paediatric medicine. *Br J Anaesth* 2001; **86:** 329–331.
92 Williams DG, Patel A, Howard RF. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* 2002; **89:** 839–845.
93 Fisher DM, Birmingham PK, Cote CJ. Rectal acetaminophen pharmacokinetics. *Anesthesiology* 1998; **88:** 1131–1132.
94 Wright PM. Population based pharmacokinetic analysis: why do we need it; what is it; and what has it told us about anaesthetics? *Br J Anaesth* 1998; **80:** 488–501.
95 Whiting B, Kelman AW, Grevel J. Population pharmacokinetics. Theory and clinical application. *Clin Pharmacokinet* 1986; **11:** 387–401.
96 Holford NHG. *MK MODEL Manual*. Cambridge, UK: Biosoft, 1994.
97 Anderson BJ, Holford NHG, Woollard GA *et al.* Paracetamol plasma and cerebrospinal fluid pharmacokinetics in children. *Br J Clin Pharmacol* 1998; **46:** 237–243.
98 Brown RD, Wilson JT, Kearns GL *et al.* Single-dose pharmacokinetics of ibuprofen and acetaminophen in febrile children. *J Clin Pharmacol* 1992; **32:** 231–241.
99 Mandema JW, Stanski DR. Population pharmacodynamic model for ketorolac analgesia. *Clin Pharmacol Ther* 1996; **60:** 619–635.
100 Boni J, Korth-Bradley J, McGoldrick K *et al.* Pharmacokinetic and pharmacodynamic action of etodolac in patients after oral surgery. *J Clin Pharmacol* 1999; **39:** 729–737.
101 Day RO, Furst DE, Dromgoole SH *et al.* Relationship of serum naproxen concentration to efficacy in rheumatoid arthritis. *Clin Pharmacol Ther* 1982; **31:** 733–740.
102 Day RO, Francis H, Vial J *et al.* Naproxen concentrations in plasma and synovial fluid and effects on prostanoid concentrations. *J Rheumatol* 1995; **22:** 2295–2303.
103 Bertin P, Lapicque F, Payan E *et al.* Sodium naproxen: concentration and effect on inflammatory response mediators in human rheumatoid synovial fluid. *Eur J Clin Pharmacol* 1994; **46:** 3–7.
104 Suri A, Estes KS, Geisslinger G *et al.* Pharmacokinetic-pharmacodynamic relationships for analgesics. *Int J Clin Pharmacol Ther* 1997; **35:** 307–323.
105 Anderson B, Anderson M, Hastie B. Paracetamol prescribing habits in a children's hospital. *N Z Med J* 1996; **109:** 376–378.
106 Miner DJ, Kissinger PT. Evidence for the involvement of N-acetyl-p-Quinoneimine in acetaminophen poisoning. *Ann Rev Pharmacol Toxicol* 1983; **12:** 251.
107 Slattery JT, Nelson SD, Thummel KE. The complex interaction between ethanol and acetaminophen. *Clin Pharmacol Ther* 1996; **60:** 241–246.
108 Nahata MC, Powell DA, Durrell DE *et al.* Acetaminophen accumulation in pediatric patients after repeated therapeutic doses. *Eur J Clin Pharmacol* 1984; **27:** 57–59.
109 Slattery JT, Wilson JM, Kalhorn TF *et al.* Dose-dependent pharmacokinetics of acetaminophen: evidence of glutathione depletion in humans. *Clin Pharmacol Ther* 1987; **41:** 413–418.
110 Kearns GL, Leeder JS, Wasserman GS. Acetaminophen overdose with therapeutic intent. *J Pediatr* 1998; **132:** 5–8.
111 Alonso EM, Sokol RJ, Hart J *et al.* Fulminant hepatitis associated with centrilobular necrosis in young children. *J Pediatr* 1995; **127:** 888–894.
112 Heubi JE, Bien JP. Acetaminophen use in children: more is not better. *J Pediatr* 1997; **130:** 175–177.
113 Heubi JE, Barbacci MB, Zimmerman HJ. Therapeutic misadventures with acetaminophen: hepatoxicity after multiple doses in children. *J Pediatr* 1998; **132:** 22–27.
114 Rivera Penera T, Gugig R, Davis J *et al.* Outcome of acetaminophen overdose in pediatric patients and factors contributing to hepatotoxicity. *J Pediatr* 1997; **130:** 300–304.
115 Hynson JL, South M. Childhood hepatotoxicity with paracetamol doses less than 150 mg/kg per day. *Med J Aust* 1999; **171:** 497.
116 Miles FK, Kamath R, Dorney SFA *et al.* Accidental paracetamol overdosing and fulminant hepatic failure in children. *Med J Aust* 1999; **171:** 472–475.
117 Morton NS, Arana A. Paracetamol-induced fulminant hepatic failure in a child after 5 days of therapeutic doses. *Paed Anaesth* 1999; **9:** 463–465.
118 Kozer E, Barr J, Bulkowstein M *et al.* A prospective study of multiple supratherapeutic acetaminophen doses in febrile children. *Vet Hum Toxicol* 2002; **44:** 106–109.
119 Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; **55:** 871–876.
120 Prescott LF, Wright N, Roscoe P *et al.* Plasma paracetamol half-life and hepatic necrosis in patients with paracetamol overdose. *Lancet* 1971; **1:** 519–522.
121 Anderson BJ, Holford NHG, Armishaw JC *et al.* Predicting concentrations in children presenting with acetaminophen overdose. *J Pediatrics* 1999; **135:** 290–295.

122 Mohler CR, Nordt SP, Williams SR *et al.* Prospective evaluation of mild to moderate pediatric acetaminophen exposures. *Ann Emerg Med* 2000; **35:** 239–244.
123 Mancini RE, Sonawane BR, Yaffe SJ. Developmental susceptibility to acetaminophen toxicity. *Res Commun Chem Pathol Pharmacol* 1980; **27:** 603–606.
124 Rumack BH. Acetaminophen overdose in children and adolescents. *Pediatr Clin North Am* 1986; **33:** 691–701.
125 Lauterburg BH, Vaishnav Y, Stillwell WG *et al.* The effects of age and glutathione depletion on hepatic glutathione turnover in vivo determined by acetaminophen probe analysis. *J Pharmacol Exp Ther* 1980; **213:** 54–58.
126 Roberts I, Robinson MJ, Mughal MZ *et al.* Paracetamol metabolites in the neonate following maternal overdose. *Br J Clin Pharmacol* 1984; **18:** 201–206.
127 Levy G, Garrettson LK, Soda DM. Evidence of placenta transfer of acetaminophen. *Pediatrics* 1975; **55:** 895.
128 Lederman S, Fysh WJ, Tredger M *et al.* Neonatal paracetamol poisoning: treatment by exchange transfusion. *Arch Dis Child* 1983; **58:** 631–633.
129 Kam PC, See AU. Cyclo-oxygenase isoenzymes: physiological and pharmacological role. *Anaesthesia* 2000; **55:** 442–449.
130 Simon AM, Manigrasso MB, O'Connor JP. Cyclo-oxygenase 2 function is essential for bone fracture healing. *J Bone Miner Res* 2002; **17:** 963–976.
131 Lipsky PE, Brooks P, Crofford LJ *et al.* Unresolved issues in the role of cyclooxygenase-2 in normal physiologic processes and disease. *Arch Intern Med* 2000; **160:** 913–920.
132 McCrory CR, Lindahl SG. Cyclooxygenase inhibition for postoperative analgesia. *Anesth Analg* 2002; **95:** 169–176.
133 Brater DC, Harris C, Redfern JS *et al.* Renal effects of COX-2-selective inhibitors. *Am J Nephrol* 2001; **21:** 1–15.
134 Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *JAMA* 1995; **273:** 929–933.
135 Lesko SM, Mitchell AA. Renal function after short-term ibuprofen use in infants and children. *Pediatrics* 1997; **100:** 954–957.
136 Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics* 1999; **104:** e39.
137 Houck CS, Wilder RT, McDermott JS *et al.* Safety of intravenous ketorolac therapy in children and cost savings with a unit dosing system. *J Pediatr* 1996; **129:** 292–296.
138 Flato B, Vinje O, Forre O. Toxicity of antirheumatic and anti-inflammatory drugs in children. *Clin Rheumatol* 1998; **17:** 505–510.
139 Szer IS, Goldenstein-Schainberg C, Kurtin PS. Paucity of renal complications associated with nonsteroidal antiinflammatory drugs in children with chronic arthritis. *J Pediatr* 1991; **119:** 815–817.
140 van Biljon G. Reversible renal failure associated with ibuprofen in a child. A case report. *S Afr Med J* 1989; **76:** 34–35.
141 Moghal NE, Hulton SA, Milford DV. Care in the use of ibuprofen as an antipyretic in children. *Clin Nephrol* 1998; **49:** 293–295.
142 Primack WA, Rahman SM, Pullman J. Acute renal failure associated with amoxicillin and ibuprofen in an 11-year-old boy. *Pediatr Nephrol* 1997; **11:** 125–126.
143 Buck ML, Norwood VF. Ketorolac-induced acute renal failure in a previously healthy adolescent. *Pediatrics* 1996; **98:** 294–296.
144 Forrest JB, Heitlinger EL, Revell S. Ketorolac for postoperative pain management in children. *Drug Saf* 1997; **16:** 309–329.
145 Ray PE, Rigolizzo D, Wara DR *et al.* Naproxen nephrotoxicity in a 2-year-old child. *Am J Dis Child* 1988; **142:** 524–525.
146 Sheiner PA, Mor E, Chodoff L *et al.* Acute renal failure associated with the use of ibuprofen in two liver transplant recipients on FK506. *Transplantation* 1994; **57:** 1132–1133.
147 Kovesi TA, Swartz R, MacDonald N. Transient renal failure due to simultaneous ibuprofen and aminoglycoside therapy in children with cystic fibrosis. *N Engl J Med* 1998; **338:** 65–66.
148 Feldman M, McMahon AT. Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity? *Ann Intern Med* 2000; **132:** 134–143.
149 Silverstein FE, Faich G, Goldstein JL *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000; **284:** 1247–1255.
150 Bombardier C, Laine L, Reicin A *et al.* Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000; **343:** 1520–1528.
151 Keenan GF, Giannini EH, Athreya BH. Clinically significant gastropathy associated with nonsteroidal antiinflammatory drug use in children with juvenile rheumatoid arthritis. *J Rheumatol* 1995; **22:** 1149–1151.
152 Dowd JE, Cimaz R, Fink CW. Nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children. *Arthritis Rheum* 1995; **38:** 1225–1231.
153 Mulberg AE, Linz C, Bern E *et al.* Identification of nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children with juvenile rheumatoid arthritis. *J Pediatr* 1993; **122:** 647–649.
154 Souter AJ, Fredman B, White PF. Controversies in the perioperative use of nonsteroidial antiinflammatory drugs. *Anesth Analg* 1994; **79:** 1178–1190.
155 Rusy LM, Houck CS, Sullivan LJ *et al.* A double-blind evaluation of ketorolac tromethamine versus acetaminophen in pediatric tonsillectomy: analgesia and bleeding. *Anesth Analg* 1995; **80:** 226–229.
156 Niemi TT, Taxell C, Rosenberg PH. Comparison of the effect of intravenous ketoprofen, ketorolac and diclofenac on platelet function in volunteers. *Acta Anaesthesiol Scand* 1997; **41:** 1353–1358.
157 Niemi TT, Backman JT, Syrjala MT *et al.* Platelet dysfunction after intravenous ketorolac or propacetamol. *Acta Anaesthesiol Scand* 2000; **44:** 69–74.
158 Bean-Lijewski JD, Hunt RD. Effect of ketorolac on bleeding time and postoperative pain in children: a double-blind, placebo-controlled comparison with meperidine. *J Clin Anesth* 1996; **8:** 25–30.
159 Watcha MF, Jones MB, Lagueruela RG *et al.* Comparison of ketorolac and morphine as adjuvants during pediatric surgery. *Anesthesiology* 1992; **76:** 368–372.
160 Sutters KA, Shaw BA, Gerardi JA *et al.* Comparison of morphine patient-controlled analgesia with and without ketorolac for postoperative analgesia in pediatric orthopedic surgery. *Am J Orthop* 1999; **28:** 351–358.
161 Lieh-Lai MW, Kauffman RE, Uy HG *et al.* A randomized comparison of ketorolac tromethamine and morphine for

postoperative analgesia in critically ill children. *Crit Care Med* 1999; **27:** 2786–2791.
162 Splinter WM, Rhine EJ, Roberts DW *et al.* Preoperative ketorolac increases bleeding after tonsillectomy in children. *Can J Anaesth* 1996; **43:** 560–563.
163 Gallagher JE, Blauth J, Fornadley JA. Perioperative ketorolac tromethamine and postoperative hemorrhage in cases of tonsillectomy and adenoidectomy. *Laryngoscope* 1995; **105:** 606–609.
164 Judkins JH, Dray TG, Hubbell RN. Intraoperative ketorolac and posttonsillectomy bleeding. *Arch Otolaryngol Head Neck Surg* 1996; **122:** 937–940.
165 Agrawal A, Gerson CR, Seligman I *et al.* Postoperative hemorrhage after tonsillectomy: use of ketorolac tromethamine. *Otolaryngol Head Neck Surg* 1999; **120:** 335–339.
166 Romsing J, Ostergaard D, Walther-Larsen S *et al.* Analgesic efficacy and safety of preoperative versus postoperative ketorolac in paediatric tonsillectomy. *Acta Anaesthesiol Scand* 1998; **42:** 770–775.
167 Strom BL, Berlin JA, Kinman JL *et al.* Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study. *JAMA* 1996; **275:** 376–382.
168 Nikanne E, Kokki H, Tuovinen K. Comparison of perioperative ketoprofen 2.0 mg kg^{-1} with 0.5 mg kg^{-1} i.v. in small children during adenoidectomy. *Br J Anaesth* 1997; **79:** 606–608.
169 Nikanne E, Kokki H, Tuovinen K. IV perioperative ketoprofen in small children during adenoidectomy. *Br J Anaesth* 1997; **78:** 24–27.
170 Kokki H, Nikanne E, Tuovinen K. I.v. intraoperative ketoprofen in small children during adenoidectomy: a dose-finding study. *Br J Anaesth* 1998; **81:** 870–874.
171 Thiagarajan J, Bates S, Hitchcock M *et al.* Blood loss following tonsillectomy in children. A blind comparison of diclofenac and papaveretum. *Anaesthesia* 1993; **48:** 132–135.
172 Walmsley AJ. Peri-operative use of nonsteroidal anti-inflammatory drugs in children. *Anaesthesia* 1997; **52:** 1120.
173 Romsing J, Ostergaard D, Drozdziewicz D *et al.* Diclofenac or acetaminophen for analgesia in paediatric tonsillectomy outpatients. *Acta Anaesthesiol Scand* 2000; **44:** 291–295.
174 Harley EH, Dattolo RA. Ibuprofen for tonsillectomy pain in children: efficacy and complications. *Otolaryngol Head Neck Surg* 1998; **119:** 492–496.
175 St Charles CS, Matt BH, Hamilton MM *et al.* A comparison of ibuprofen versus acetaminophen with codeine in the young tonsillectomy patient. *Otolaryngol Head Neck Surg* 1997; **117:** 76–82.
176 Holford NHG. The target concentration approach to clinical drug development. *Clin Pharmacokinet* 1995; **29:** 287–291.
177 Holford NHG. Target concentration intervention: beyond Y2K. *Brit J Clin Pharmacol* 1999; **48:** 9–13.
178 van Lingen RA, Simons SH, Anderson BJ *et al.* The effects of analgesia in the vulnerable infant during the perinatal period. *Clin Perinatol* 2002; **29:** 511–534.
179 Berger RG. Intelligent use of NSAIDs – where do we stand? *Expert Opin Pharmacother* 2001; **2:** 19–30.
180 Jackson LM, Hawkey CJ. COX-2 selective nonsteroidal anti-Inflammatory drugs: do they really offer any advantages? *Drugs* 2000; **59:** 1207–1216.

Accepted 1 May 2003