The pharmacokinetics of postoperative intravenous ketorolac tromethamine in children

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Ketorolac tromethamine (0.5 mg kg^{-1}) was given intravenously to 10 children (age 4–8 years) after minor surgery. Values of steady-state volume of distribution and plasma clearance were approximately two times higher than those in adults but values of elimination half-life were similar.

Keywords ketorolac tromethamine pharmacokinetics children

Introduction

Ketorolac tromethamine is a non-steroidal anti-inflammatory analgesic, which has been shown to be effective for the treatment of moderate to severe pain (Bloomfield *et al.*, 1986; Yee *et al.*, 1986). Its pharmacokinetics have been studied in adults (Jung *et al.*, 1988; Mroszczak *et al.*, 1987) but not in children. The present study investigated the kinetics of ketorolac tromethamine administered intravenously to small children.

Methods

We obtained informed consent from the parents and institutional approval to study 10 patients undergoing strabismus surgery. Children considered to be poor anaesthetic risks were excluded from the study.

Administration of ketorolac tromethamine and anaesthetic procedure

The same premedication and anaesthetic technique was used for all patients. Oral flunitrazepam was given for premedication 0.1 mg kg^{-1} (maximally 2 mg). A vein on the dorsum of one hand was cannulated for the administration of intravenous anaesthetics. After induction of anaesthesia another vein on the contralateral hand was cannulated for blood sampling. Prior to induction of anaesthesia 0.005 mg kg^{-1} of glycopyrrolate was administered intravenously. Anaesthesia was induced with thiopentone $2\text{--}5 \text{ mg kg}^{-1}$ and intubation was facilitated with $1.0\text{--}1.5 \text{ mg kg}^{-1}$ of suxamethonium. For maintenance of anaesthesia nitrous oxide/oxygen (7 : 3), halothane and pancuronium were used. The patients were normoventilated with the Servo[®] 900 ventilator (Siemens-Elema Inc., Sweden). At the end of surgery

the residual neuromuscular blockade was reversed with 0.04 mg kg^{-1} of neostigmine and 0.01 mg kg^{-1} of glycopyrrolate. The patients were extubated and transferred to the recovery room. During the study period arterial pressure, heart rate, and ventilation were recorded at 15 min intervals for 2 h and then at the time of blood sampling. Sedation and pain scores were also recorded (Maunuksela *et al.*, 1987).

Ketorolac tromethamine 0.5 mg kg^{-1} corresponding to 0.34 mg kg^{-1} of free acid was given as a bolus intravenous injection. Additional buprenorphine was given for postoperative pain 0.003 mg kg^{-1} intravenously in the recovery room and 0.005 mg kg^{-1} sublingually on the ward according to clinical needs. Blood samples (2 ml) were taken immediately prior to administration of ketorolac tromethamine and after 2, 5, 10, 15, 30, 45, 60 min and 2, 4, 6–8 and 16–20 h. Blood was collected into heparinized tubes. The plasma was separated immediately and stored at -20°C until analysis.

Assay of ketorolac tromethamine and pharmacokinetic analysis

The concentration of ketorolac in plasma was measured by high performance liquid chromatography with u.v. detection (Wu *et al.*, 1986). The minimum assayable amount of ketorolac was $10 \mu\text{g l}^{-1}$. The coefficient of variation of repeated determinations was better than 5%. The individual plasma drug concentration-time profiles were fitted by biexponential and triexponential functions using nonlinear least-squares regression (Metzler & Weiner, 1985). A weighting value of $1/c^2$ was used. The goodness of the fit was determined by comparison of the sum of squares of weighted residual errors, and by assessment of randomness of 'scatter' of

actual data points about the fitted function (Boxenbaum *et al.*, 1974). Final estimates of the terminal exponential rate constants of the fitted function were used to calculate elimination half-lives ($t_{1/2,z}$). Plasma clearance (CL) and volume of distribution at steady-state (V_{ss}) were calculated according to standard methods using noncompartmental analysis based on statistical moment theory (Gibaldi & Perrier, 1982).

Results

The time course of plasma drug concentrations is shown in Figure 1. A triexponential function gave the best fit in all patients. The correlation coefficients between predicted and measured concentrations were better than 0.997 in all patients (mean 0.999). The mean estimated $t_{1/2,z}$ was 6.1 h and mean CL was $0.70 \text{ ml kg}^{-1} \text{ min}^{-1}$. V_{ss} varied from 0.19 to 0.44 l kg^{-1} . CL, V_{ss} and $t_{1/2,z}$ were not correlated with age, weight or body surface area. Characteristics of the patients and the calculated pharmacokinetic parameters are summarized in Table 1.

Four children were given no additional analgesics in the recovery room. Six children received additional analgesia at 1.3–6.4 h (mean 2.4 h). In the dose used ketorolac tromethamine did not cause clinically significant changes in blood pressure, heart rate or respiratory rate. Apart from local irritation at the injection site no side-effects were observed.

Discussion

The terminal elimination half-lives of ketorolac varied from 3.5 to 10 h although most values were between 5 and 7 h. The mean value was 6.1 h which is similar to that observed in adults. In adults ketorolac is extensively bound to plasma proteins contributing to a relatively low volume of distribution. In children V_{ss} was approximately two times higher than that in adults (Jung *et al.*, 1988; Mrosczak *et al.*, 1987). Ketorolac is a water-soluble drug. Thus, the relatively higher volume of body water in children may partially explain this differ-

ence in volume of distribution. Another possibility is that in children ketorolac is less extensively bound to plasma proteins.

The mean CL of ketorolac was $0.70 \text{ ml kg}^{-1} \text{ min}^{-1}$ which is about two times higher than in adults (Jung *et al.*, 1988; Mrosczak *et al.*, 1987). This is in agreement with previous studies of the pharmacokinetics of various drugs in different age groups (MacLeod & Radde, 1985). A less extensive binding of ketorolac to plasma proteins would also explain the higher CL of ketorolac in children. Ketorolac is excreted predominantly (92%) into the urine with 56% of the recovery being in the form of unchanged drug (Mrosczak *et al.*, 1987). An increase of the free fraction of ketorolac in plasma would thus augment its glomerular filtration and increase excretion if tubular reabsorption does not counteract the change (Gibaldi & Koup, 1981). Because the hepatic CL of ketorolac is low (Mrosczak *et al.*, 1987) it will be directly proportional to the unbound fraction of drug in plasma.

In conclusion, values of V_{ss} and CL were approximately two times higher than those in adults, but values of $t_{1/2,z}$ were similar. Because the elimination half-life of a drug is directly proportional to volume of distribution and inversely proportional to CL the lack of change in elimination half-life is explained. Since the half-life is unchanged, the dosing interval for children need not be altered relative to adults. The higher CL of ketorolac in children may necessitate higher maintenance doses on a dose per weight basis than in adults if there is the same relationship in adults and children between plasma total ketorolac concentration and pain relief.

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Table 1 Characteristics of the patients and the pharmacokinetic parameters of ketorolac following an intravenous injection of 0.5 mg kg^{-1} of ketorolac tromethamine

Patient number/ gender	Age (years)	Weight (kg)	$t_{1/2,z}$ (h)	V_{ss} (l kg^{-1})	CL ($\text{ml kg}^{-1} \text{ min}^{-1}$)
1/M	6.8	19.9	3.5	0.20	0.96
2/M	8.1	24.0	5.9	0.25	0.62
3/F	5.4	20.4	10.0	0.44	0.77
4/F	5.4	20.0	6.4	0.30	0.72
5/M	6.2	19.4	6.9	0.24	0.50
6/M	6.5	21.0	5.5	0.19	0.58
7/F	7.4	23.3	5.9	0.20	0.58
8/F	4.8	19.6	3.6	0.21	0.84
9/F	5.2	16.2	8.2	0.34	0.78
10/F	4.3	19.9	5.5	0.25	0.67
Mean	6.0	20.4	6.1	0.26	0.70
s.d.	1.2	2.2	1.9	0.07	0.14

Figure 1 Plasma ketorolac concentrations after intravenous administration of ketorolac tromethamine (0.5 mg kg^{-1}) to 10 children.

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