Enantiomer-selective pharmacokinetics and metabolism of ketorolac in children

Objective: **To compare the pharmacokinetics and metabolism of *R*(+)- and *S*(−)- ketorolac in children.**
Methods: **Children from 3 to 18 years old received 0.6 mg/kg racemic ketorolac intravenously. Serial blood samples were obtained for 12 hours, and urine was collected for 12 to 24 hours. Racemic ketorolac was measured in plasma, and racemic ketorolac, *para*-hydroxyketorolac, and ketorolac glucuronide were measured in urine by HPLC. *S*(−)- and *R*(+)-ketorolac were measured in plasma; *S*(−)- and *R*(+)-ketorolac and ketorolac glucuronide were measured in urine by chiral HPLC separation. Plasma pharmacokinetic parameters for racemic drug and both enantiomers were determined for each patient.**
Results: **Clearance of racemic ketorolac in children was approximately 2 times the clearance reported in adults. Clearance of the *S*(−) enantiomer was 4 times that of the *R*(+) enantiomer. Terminal half-life of *S*(−)-ketorolac was 40% that of the *R*(+) enantiomer, and the apparent volume of distribution of the *S*(−) enantiomer was greater than that of the *R*(+) form. Recovery of *S*(−)-ketorolac glucuronide was 2.3 times that of the *R*(+) enantiomer.**
Conclusion: **The higher clearance in children suggests that the weight-adjusted dose of ketorolac may have to be greater for children to achieve plasma concentrations comparable to those of adults. Because of the greater clearance and shorter half-life of *S*(−)-ketorolac, pharmacokinetic predictions based on racemic assays may overestimate the duration of pharmacologic effect. Enantiomeric pharmacokinetic differences are best explained by stereoselective plasma protein binding. Selective glucuronidation of the *S*(−) enantiomer suggests that stereoselective metabolism may also be a contributing factor. (Clin Pharmacol Ther 1999;65:382-8.)**

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Ketorolac is the only nonsteroidal anti-inflammatory drug currently available in the United States for parenteral administration. It is supplied and administered as a racemic mixture that contains a 1:1 ratio of the *R*(+) and *S*(−) stereoisomers. Pharmacologic activity resides almost exclusively with the *S*(−) stereoisomer. Analgesic efficacy of ketorolac has been established in clinical trials in adults[1,2] and published studies in children.[3-8] Although not approved by the Food and Drug Administration for pediatric use, ketorolac is widely used off-label as a parenteral analgesic in children. However, in contrast to the adult population, there is a paucity of information regarding the pharmacokinetics and metabolism of ketorolac in children of different ages. Furthermore, there is no previously published information on the chiral pharmacokinetics or metabolism of the drug in children. Consequently, pediatric doses have been derived empirically through clinical experience with little pharmacokinetic basis. We studied the racemic and chiral pharmacokinetics and metabolism of ketorolac in a group of children enrolled in a randomized double-blind comparison of ketorolac with morphine for postsurgical pain.

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METHODS

Patients. Children from 3 to 18 years old with normal renal and hepatic function who required postsurgi-

cal analgesia were eligible for enrollment. Patients with known kidney disease, liver disease, bleeding abnormalities, gastrointestinal abnormalities, dehydration, hypovolemia, heart failure, or aspirin or nonsteroidal anti-inflammatory drug–induced bronchospasm were excluded. In addition, patients receiving methotrexate, thiazide diuretics, β-blocking drugs, or warfarin at the time of study were excluded. Informed written permission was obtained from the parent(s) or guardian of each child before enrollment, and assent was obtained from children ≥7 years old when the child was cognitively competent for age. The study was approved by the Institutional Review Board of the Children's Hospital of Michigan.

Dosing. After enrollment, each patient was randomly assigned to receive a single dose of either morphine or ketorolac as the first postoperative analgesic after he or she arrived in the critical care unit. Patients who were randomized to receive ketorolac were given a single 0.6 mg/kg dose of racemic ketorolac tromethamine infused intravenously with a syringe pump over a 10-minute period. Medication was infused through microbore tubing inserted into a port that did not exceed a distance of 12 inches from the insertion site of the intravenous canula. The medication infusion was followed by a 5 mL normal saline solution flush.

Pharmacokinetic sampling. Two-milliliter venous blood samples were drawn into ethylenediaminetetraacetic acid tubes from a site contralateral to the infusion site. Samples were obtained before the dose and at 10, 15, 30, and 60 minutes, hourly from 1 to 6 hours, and at 8 and 12 hours timed from the beginning of the infusion. Total blood loss did not exceed 24 mL in any child and comprised less than 1% of total blood volume for most children. Plasma was separated and frozen at –80°C until assay was performed. Urine was quantitatively collected for 12 to 24 hours after the dose was administered. Urine was kept on ice at 3°C throughout the collection to minimize spontaneous hydrolysis of the glucuronide conjugate. At completion of the collection the volume was immediately measured, and an aliquot was frozen and maintained at –80°C until the assay was performed.

Racemic assays. Racemic ketorolac in plasma and racemic ketorolac and *para*-hydroxyketorolac in urine were measured by HPLC. All assays were performed in duplicate with a full set of analytical standards. Authentic racemic ketorolac and *para*-hydroxyketorolac analytical standards were provided by Syntex Research (Palo Alto, Calif).

Plasma analytical standards were prepared in blank plasma over the full range of clinical plasma concentrations. One hundred microliters plasma or analytical standard was diluted with 200 μL sodium acetate buffer (pH = 6.0) and extracted with 1 mL ethyl acetate that contained ethylthiobarbituric acid as the internal standard. The organic phase was separated and dried under nitrogen. The residue was reconstituted in 100 μL mobile phase and injected onto a Waters C_{18} MicroBondapak 5 μm reversed-phase column. Mobile phase was 35% acetonitrile in a 0.05 mol/L sodium acetate buffer at pH 6.0 with flow rate of 1 to 2 mL/min. Effluent was monitored at 313 nm. The limit of quantitation was 5 ng/mL, with a linear response across the full range of concentrations and coefficient of variation of <10%.

Urine analytical standards that contained authentic ketorolac and *para*-hydroxyketorolac were prepared in fresh blank urine. Chromatographic conditions were similar to those for plasma, except the mobile phase was 18% acetonitrile in acetate buffer at pH 6.5 to accomplish baseline separation of ketorolac and *para*-hydroxyketorolac. Chromatographs were obtained for each set of samples with standard curves for ketorolac and *para*-hydroxyketorolac and were analyzed in duplicate. Assays of urine samples were obtained with and without hydrolysis with β-glucuronidase to estimate concentration of glucuronidated drug. Bovine β-glucuronidase (Sigma Chemical Co, St Louis, Mo) was reconstituted in 0.05 mol/L acetate buffer (pH = 6.5) at a concentration of 5000 Fishman units/mL. Aliquots of each urine sample were diluted 1:10 in either buffer, β-glucuronidase, or β-glucuronidase plus sacarolactone (a specific β-glucuronidase inhibitor). Samples were incubated at 37°C for 12 hours. Preliminary experiments were conducted to establish the conditions that provided complete stoichiometric hydrolysis of the glucuronides. After incubation was performed, samples were centrifuged and 10 μL supernatant was injected on column. Concentration of glucuronidated drug was estimated from the difference in measured concentration with and without hydrolysis.

Chiral assays. Authentic *R*(+)- and *S*(–)-ketorolac analytical standards were prepared by Chiral Technologies (Exton, Pa) by preparative chiral HPLC separation of racemic ketorolac acid. Authenticity and purity of the respective chiral standards were confirmed by x-ray crystallography. Standard concentrations of both enantiomers were prepared in plasma and urine, respectively, over the anticipated concentration range.

One hundred microliters of plasma or analytical standard prepared in plasma was diluted in 200 μL sodium acetate buffer and extracted into 1.0 mL ethyl acetate that contained *S*(+)-6-methoxy α-methyl-2-naphthalene

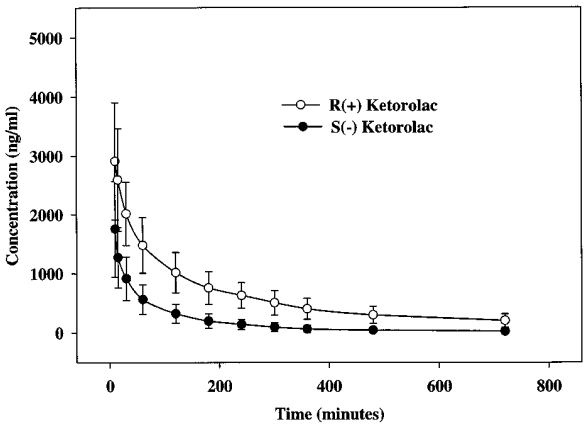

Figure 1. Comparison of plasma concentrations of *R*(+)- and *S*(–)- ketorolac after 0.6 mg/kg dose of racemic ketorolac administered intravenously over 10-minute period. Area under the concentration versus time curve of the enantiomers extrapolated to infinity is significantly different ($P < .001$). All points represent mean ± SD; n = 47.

acetic acid as the internal standard. The organic phase was separated and dried under nitrogen, after which the sample residue was reconstituted in 100 μL mobile phase and injected on column. *R*(+)-Ketorolac and *S*(–)-ketorolac were quantitatively separated on a Chiracel OJ-R chiral column (Chiral Technologies). Mobile phase was 45% acetonitrile in 3 mmol/L perchloric acid, pH 2.0, with 1.2 mL/min flow. Effluent was monitored at 313 nm. Racemization of ketorolac may occur during indirect racemic assays that require precolumn derivatization under strong basic conditions, leading to spurious results.[9] Such conditions were avoided with the direct chiral separation used in this study.

Urine samples were subjected to chiral assay with and without β-glucuronidase hydrolysis as described previously for the racemic assay. Concentration of both glucuronidated enantiomers was estimated from the difference in measured concentration with and without hydrolysis.

The chiral assay provided baseline resolution of the respective analyte peaks, with *R*(+)-ketorolac eluting at 3.0 minutes, *S*(–)-ketorolac at 3.5 minutes, and the internal standard at 5.8 minutes. Limit of quantitation was 5 ng/mL with a coefficient of variation <10%.

Pharmacokinetic analysis. PKAnalyst software (MicroMath Scientific Software, Salt Lake City, Utah) was used to estimate plasma pharmacokinetic parameters for each patient from a nonlinear least-squares fit of plasma concentrations of racemic ketorolac and both ketorolac enantiomers versus time. Data were fitted to a biexponential or triexponential model with a 10-minute zero-order infusion function. Best statistical fit was determined from the Akaike information criterion. Data from most of the patients was best fitted with a biexponential function, although data from several patients best fitted a triexponential equation. Area under the concentration versus time curve [AUC(0-12)] was integrated with the trapezoid method. Total area [AUC(0-∞)] was calculated by summation of AUC(0-12) + Cp_{12}/λ_n, in which Cp_{12} is the ketorolac plasma concentration at 12 hours and λ is the terminal elimination rate constant. Clearance was calculated by the following: Dose/AUC(0-∞); and apparent volume of distribution (V_d) was calculated from the equation: Dose/AUC × λ_n. Total racemic ketorolac, *para*-hydroxyketorolac, and ketorolac glucuronide excreted in urine were determined by multiplying their respective concentrations by the total urine collection volume. Total drug excreted was computed from the sum of the 3 measured components. Fraction of dose recovered in urine was determined by dividing the quantity of each compound by the total dose. Analogous values were computed for both ketorolac enantiomers and their respective glucuronides. Unfortunately, analytical standards for the individual *para*-hydroxyketorolac enantiomers were not available, so they could not be quantitated in urine.

Statistical analysis. Pharmacokinetic and metabolic data were summarized with descriptive statistics. Parametric methods for comparison of mean values and correlation statistics were used when appropriate to compare pharmacokinetic and metabolic characteristics of *R*(+)- and *S*(–)-ketorolac. Categorical data were evaluated with appropriate tests for proportions. Null hypotheses were rejected if $\alpha \leq 0.05$.

RESULTS

Demographics. Racemic ketorolac plasma and urine data were available from 50 children with a median age of 11.6 years (age range, 3 to 18 years). Patients were well distributed across the age range, with 11 between 3 to 6 years, 23 between 6 to 12 years, and 16 between 12 to 18 years. Fifty-four percent were female. Plasma kinetic data on ketorolac enantiomers were obtained from 47 children with a median age of 11.7 years. Fifty-five percent were female. Analysis of *R*(+)- and *S*(–)-ketorolac and the respective glucuronides in urine was possible in 45 children with a median age of 12 years; 49% were female. Sufficient plasma to complete chiral analysis was not available from 3 children, and sufficient urine was not available from 5 children.

Table I. Pharmacokinetics of racemic ketorolac (n = 50)

C_{max} (ng/mL)	4698 ± 1641
V_d (L/Kg)	0.35 ± 0.2
$t_{½}\alpha$ (min)	28.7 ± 20.7
$t_{½}\lambda$ (min)	243 ± 137
Plasma CL (mL/min/kg)	1.1 ± 0.5

Data are mean values ± SD.
C_{max}, Maximum plasma concentration; V_d, apparent volume of distribution; $t_{½}\alpha$, distribution half-life; $t_{½}\lambda$, terminal elimination half-life; CL, clearance.

Table II. Urinary recovery of racemic ketorolac (n = 50)

Drug or metabolite	*Percent of dose*	*Percent of total drug recovered*
Ketorolac	23.4 ± 9.7	57 ± 11.7
para-Hydroxyketorolac	10.5 ± 8.5	22 ± 11.1
Ketorolac glucuronide	10.3 ± 5.9	21 ± 9.8
Total ketorolac	43.5 ± 13.7	100

Data are mean values ± SD.

The most common diagnosis (26 of 50) was congenital heart disease in children undergoing elective cardiac surgical procedures. The next most common diagnosis (12 of 50) was scoliosis in children undergoing corrective spinal surgery. Six children underwent surgical procedures for malignancy and 2 for facial reconstructive surgery; 4 were coded as "other."

Urine was collected for 12 hours in 13 children, 16 hours in 2, 17 hours in 2, 18, 19, and 20 hours, respectively, in 1 patient each, 21 hours in 2, 22 hours in 3, 23 hours in 2, and 24 hours in 18. We were concerned that the variable collection intervals might influence recovery of drug in the urine. However, the mean percentage of dose recovered was not different between the 12- and 24-hour collections (P = .480), and no correlation was observed between collection interval and the percentage of dose recovered (Pearson correlation, 0.08; P = .6). Therefore we analyzed all urine data together regardless of collection interval over the range of 12 to 24 hours.

Racemic pharmacokinetics. The racemic ketorolac pharmacokinetic parameter values are summarized in Table I. These values were well within the range of those previously reported.[10-12] No relationship was observed between age and V_d and terminal half-life ($t_{½}$) or clearance across the age range of children in this study.

We recovered 43.5% ± 13.7% (SD) of the ketorolac dose in the urine as racemic drug and metabolites (Table II). Approximately 60% of total ketorolac recovered was parent drug. Ketorolac glucuronide and *para*-hydroxyketorolac each comprised approximately 20% of the remainder.

Chiral-selective pharmacokinetics. Plasma pharmacokinetics of the 2 ketorolac enantiomers differed markedly. Concentrations of the *S*(–) enantiomer were lower than those of the *R*(+) enantiomer at all time points (Figure 1). Distribution and terminal elimination $t_{½}$ values of the *S*(–) enantiomer were shorter, AUC(0-∞) was decreased, and clearance was significantly greater compared with the *R*(+) enantiomer (Table III). The AUC(0-∞) ratio of the *S*(–) to *R*(+) enantiomers was 0.25 ± 0.15.

Total recovery of *R*(+)-ketorolac expressed as a percentage of dose was 13.8% ± 5.4% compared with 14.3% ± 6.0% for *S*(–)-ketorolac. This result was not significantly different (P = .275). However, a significant difference was observed in glucuronidation of the 2 enantiomers. *S*(–)-Ketorolac glucuronide in urine, expressed as a percentage of dose was, for example, 2.3 times *R*(+)-ketorolac glucuronide: 3.6% versus 1.5%. Expressed another way, *S*(–)-ketorolac glucuronide comprised 27% of total *S*(–)-ketorolac recovered in urine, whereas *R*(+)-ketorolac glucuronide comprised only 12% of total *R*(+)-ketorolac recovered (Table IV). Unfortunately, we were unable to evaluate stereoselective *para*-hydroxylation, which theoretically also could contribute to differential metabolism of the 2 enantiomers.

DISCUSSION

The mean $t_{½}$ (4.0 hours) and plasma clearance (1.1 mL/min/kg) of racemic ketorolac in the 50 patients in this study were within the range of those reported previously. Kerr et al[11] studied racemic ketorolac kinetics in 15 children ranging in age from 1.4 to 17 years and reported a mean $t_{½}$ of 2.7 hours, with a plasma clearance of 0.9 mL/min/kg. Gonzalez-Martin et al[10] studied 14 children from 2 to 8 years old and reported a mean ketorolac $t_{½}$ of 2.3 hours, with a plasma clearance of 1.3 mL/min/kg. Olkkola and Maunuksela[12] reported a mean terminal $t_{½}$ of 6.1 hours and a mean plasma clearance of 0.7 mL/min/kg in 10 children who ranged in age from 4 to 8 years. The longer terminal $t_{½}$ reported by Olkkola and Maunuksela[12] may be in part the result of a longer sampling time and may represent elimination from a deep compartment not detected by the other studies. They measured plasma concentrations over a 20-hour period, whereas Kerr et al[11] and Gonzalez-Martin et al[10] sampled for only 6 hours. We sampled for 12 hours, assuming this would represent a minimum of 2 $t_{½}$ values, based on previously reported $t_{½}$ values in young healthy adults.[1]

With the exception of the study by Olkkola and Maunuksela,[12] the mean $t_{½}$ values reported for children

Table III. Pharmacokinetics of ketorolac enantiomers (n = 47)

Pharmacokinetic parameter	*S(–)-Ketorolac*	*R(+)-Ketorolac*
C_{max} (ng/mL)	1609 ± 751	2845 ± 1007*
V_d (L/Kg)	0.82 ± 0.38	0.50 ± 0.34*
$t_{½}\alpha$ (min)	17 ± 21	32 ± 29†
$t_{½}\lambda$ (min)	107 ± 59	259 ± 131*
AUC(0-∞) (μg · min/mL)	126 ± 63	508 ± 208*
Plasma CL (mL/min/kg)	6.2 ± 3.3	1.4 ± 0.5*

Data are mean values ± SD.

C_{max}, Maximum plasma concentration; V_d, apparent volume of distribution; $t_{½}\alpha$, distribution half-life; $t_{½}\lambda$, terminal elimination half-life; AUC(0-∞), area under the concentration–time curve extrapolated to infinity; CL, clearance.

*P < .001.

†P < .007.

Table IV. Urinary recovery of ketorolac enantiomers (n = 45)

Drug or metabolite	*Percent of dose*	*Percent of total enantiomer recovered*
R(+)-Ketorolac	12.3 ± 5.1	88 ± 9
S(–)-Ketorolac	10.7 ± 5.0	73 ± 13
R(+)-Glucuronide	1.5 ± 1.2*	12 ± 7*
S(–)-Glucuronide	3.6 ± 2.3*	27 ± 15*

Data are mean values ± SD.

*Difference between *R*(+) and *S*(–) significant, P < .001.

are shorter than the range of mean $t_{½}$ values reported in studies of healthy adults. Reported mean $t_{½}$ values in healthy young adults have ranged from 2.7 to 6.0 hours,[1,2] with prevailing values of approximately 5 hours. More striking is the difference in V_d and plasma clearance between children and adults. The mean V_d in adults was 0.17 to 0.25 L/kg,[1] whereas it was 0.21 to 0.35 L/kg in the pediatric studies. The mean plasma clearance in studies of adult volunteers[1] ranged from 0.3 to 0.55 mL/min/kg, whereas the mean plasma clearance in our 50 subjects was 1.1 mL/min/kg. Clearance in the other published pediatric studies[10-12] ranged from 0.7 to 1.3 mL/min/kg. Because of the greater plasma clearance in children, larger maintenance doses may be required than in adults to provide comparable plasma concentrations.

Recovery of racemic ketorolac in the urine of our subjects was less than that reported by Mroszczak et al[13] in 4 adult volunteers. They recovered 90% of the dose in urine after intravenous administration of ^{14}C-ketorolac. Of total radioactivity recovered, 56% was unchanged ketorolac, 11% was *para*-hydroxyketorolac, and 33% was polar metabolites, presumably glucuronidated ketorolac. Although our total recovery was less, the proportional recovery in our patients was quite similar to that in the adult study: 57% ketorolac, 22% *para*-hydroxyketorolac, and 21% ketorolac glucuronide. Decreased recovery from the children in our study may be at least partly attributable to incomplete urine collection from some children, despite our best efforts to the contrary.

The most impressive observation from this study is the marked difference between *S*(–)- and *R*(+)-ketorolac plasma kinetics, which has not been reported previously in children. Clearance of the *S*(–) enantiomer was 4 times that of the *R*(+) enantiomer. Likewise, the *S*(–) enantiomer $t_{½}$ was 40% that of the *R*(+) enantiomer, and the V_d of the *S*(–) enantiomer was significantly greater than that of the *R*(+) form. Although there are limited studies of ketorolac chiral kinetics in adults, similar observations have been reported in a small number of adult volunteers.[9,14,15] The substantially shorter $t_{½}$ of the *S*(–) enantiomer has important clinical significance because it is the active stereoisomer.[16] Assuming analgesia is related to plasma concentration, previously reported racemic plasma kinetics may grossly overestimate the duration of pharmacologic effect.

Several theoretical explanations for the greater clearance of *S*(–)-ketorolac may be considered. These include (1) in vivo inversion of *S*(–)- to *R*(+)-ketorolac, (2) stereoselective protein binding, and (3) stereoselective metabolism.

It is unlikely that in vivo inversion plays a significant role because interconversion of *S*(–)- to *R*(+)-ketorolac is negligible in humans. Mroszczak et al[15] found that only 6.5% of a dose of *S*(–)-ketorolac was converted to the *R*(+) enantiomer in adult volunteers, and there was no interconversion of *R*(+)- to *S*(–)-ketorolac.

On the other hand, stereoselective binding of nonsteroidal anti-inflammatory drugs to human serum albumin is well documented,[17] and ketorolac is no exception.[18] The unbound fraction of *S*(–)-ketorolac is more than 2-fold greater than that of *R*(+)-ketorolac over an enantiomeric plasma concentration range from 2 to 15 μg/mL. Binding of the 2 enantiomers is not affected by the presence of the corresponding antipode, although binding of both is decreased in the presence of octanoic acid.[19] Stereoselective protein binding may significantly affect pharmacokinetics of highly bound drugs with relatively low intrinsic clearance such as ketorolac for which clearance is directly proportional to the unbound fraction. Although binding differences have a modest affect on V_d, the effect on clearance is substantially greater. Correspondingly, the terminal elimination $t_{½}$ is shortened in the presence of decreased bind-

ing because $t_{½}$ is equal to the ratio of V_d to total body clearance. The shorter distribution $t_{½}$ of *S*(–)-ketorolac observed in this study is also consistent with decreased protein binding. The differences in *S*(–)- and *R*(+)-ketorolac plasma kinetics in our study can be explained by stereoselective protein binding, although chiral-selective metabolism cannot be excluded.

None of the previously published studies in adults or children has explored enantiomer-specific recovery of ketorolac metabolites in the urine. Although the data in our study are incomplete because of the unavailability of analytical standards for *S*(–)- and *R*(+)-*para*-hydroxyketorolac, we did observe a significant difference in glucuronidation of the 2 enantiomers. The amount of *S*(–)-ketorolac glucuronide in urine was 2.3 times that of the *R*(+) isomer. This result is consistent with stereoselective conjugation, which could contribute to greater clearance of *S*(–)-ketorolac. In theory, both the acid and *para*-hydroxyglucuronides may be formed. We were unable to distinguish the 2 glucuronides and therefore cannot rule out preferential glucuronidation of *S*(–)-*para*-hydroxyketorolac and *S*(–)-ketorolac. Conclusions regarding selective *para*-hydroxylation cannot be drawn from our study, and there is no other available information regarding stereoselective hydroxylation.

In conclusion, clearance of racemic ketorolac in children is approximately double the clearance of the drug in adults. This finding suggests that weight-adjusted maintenance doses may have to be greater in children to achieve comparable plasma concentrations. Although the $t_{½}$ of racemic ketorolac tends to be shorter in children, there is considerable overlap with $t_{½}$ values reported in adults, and the difference is not of a magnitude to require a decrease in the recommended dosing interval. Almost 60% of ketorolac recovered in the urine is parent drug, with *para*-hydroxyketorolac and ketorolac glucuronide comprising approximately 20% each. This result implies that ketorolac clearance will be decreased in the presence of kidney failure.

Clearance of *S*(–)-ketorolac is approximately 4 times the clearance of *R*(+)-ketorolac, resulting in much lower concentrations of the pharmacologically active *S*(–) enantiomer. The $t_{½}$ of the *S*(–) isomer is also shorter. This may have clinical implications because the $t_{½}$ of racemic ketorolac may grossly overestimate the duration of pharmacologic effect. Enantiomeric pharmacokinetic differences are best explained by stereoselective plasma protein binding. However, greater glucuronidation of the *S*(–) enantiomer suggests that stereoselective metabolism may also be a contributing factor.

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