

# PHARMACOKINETICS OF KETOROLAC PENTYL ESTER, A NOVEL ESTER DERIVATIVE OF KETOROLAC, IN RABBITS

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Ketorolac is a potent nonsteroidal anti-inflammatory drug. Recently, a novel ester of ketorolac, ketorolac pentyl ester, was synthesized. When prepared in injectable oil, the new agent demonstrated a long duration of action. Ketorolac pentyl ester was synthesized using a prodrug design by esterification of ketorolac, and appeared to be a prodrug of ketorolac *in vivo*, which needed to be confirmed. The aim of the present study was to establish the prodrug's pharmacokinetics *in vivo*, and to confirm whether or not ketorolac pentyl ester was a prodrug of ketorolac. Pharmacokinetic profiles of intravenous ketorolac and its pentyl ester on an equal-molar basis in six rabbits were evaluated. A high-performance liquid chromatographic method was used to determine the plasma concentrations of ketorolac and its pentyl ester. We found that the plasma concentrations of ketorolac pentyl ester declined rapidly after injection and so did the conversion of ketorolac pentyl ester to ketorolac. Also, the conversion of ketorolac was proved complete when compared with intravenous ketorolac under an equi-molar basis. In conclusion, this *in vivo* pharmacokinetic study confirmed that ketorolac pentyl ester was a prodrug of ketorolac.

**Key Words:** ketorolac, ketorolac pentyl ester, pharmacokinetic, prodrug  
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Most patients who experience moderate to severe pain (e.g. postoperative pain, post-traumatic pain and burn pain) often require analgesics in the first 3 days after injury [1–6]. An analgesic with a long-lasting effect of 2–3 days may be particularly valuable for these patients. Currently, opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used analgesics in these cases. To date, several long-acting opioids have been developed and/or clinically available (such as transdermal fentanyl or buprenorphine patch, long-acting ester derivatives of nalbuphine or buprenorphine) [1,2,7–9]. However, no long-acting NSAID has been developed or has been clinically available.

Among the NSAIDs, ketorolac is the most potent [3–6], with an analgesic potency comparable to some opioids and is an attractive alternative to opioids for the management of moderate to severe pain. Ketorolac is commonly used in the postoperative setting, in both hospital inpatients and outpatients, and in patients in various pain states [3–6]. Ketorolac 10–30 mg intramuscular (IM) injection has similar analgesic efficacies to those of morphine 6–12 mg and pethidine 50–100 mg IM [3–6,10–12]. Although ketorolac has a potent analgesic effect, its duration of action is relatively short (4–6 hours following 10–30 mg IM). Prolonging the duration of action would make ketorolac more clinically valuable for treating long-lasting pain.

Recently, an ester of ketorolac, ketorolac pentyl ester (Figure 1), was synthesized and evaluated [13,14]. When prepared in an injectable oil as a depot formulation and injected IM in rats, ketorolac pentyl ester was found to have a long-lasting analgesic effect that was 7.8-fold longer than the traditional saline dosage form of ketorolac,

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stream of filtered dry air. The samples were then reconstituted by 250  $\mu\text{L}$  of the mobile phase of the HPLC system. Aliquots of 200  $\mu\text{L}$  were injected into the HPLC system.

The plasma concentration-time profiles of ketorolac and its pentyl ester were fitted by using the computer program PCNONLIN (version 3.0, Statistical consultants) [15]. Akaike information criteria, weighted residual sum of squares, and residual plots were used to judge the goodness-of-fit of the model to data [16]. A CSTRIP computer program was used to obtain the initial parameter estimations, which were required for nonlinear regression analysis by the computer program PCNONLIN [15]. Pharmacokinetic parameters were calculated by standard formulae [15,16]. We compared the area under curve (AUC) of ketorolac that converted from ketorolac pentyl ester with that obtained from direct IV injection of ketorolac. The bioequivalence of these two AUCs was tested by using two one-sided  $t$  tests. A  $p$  value of less than 0.05 was considered significant.

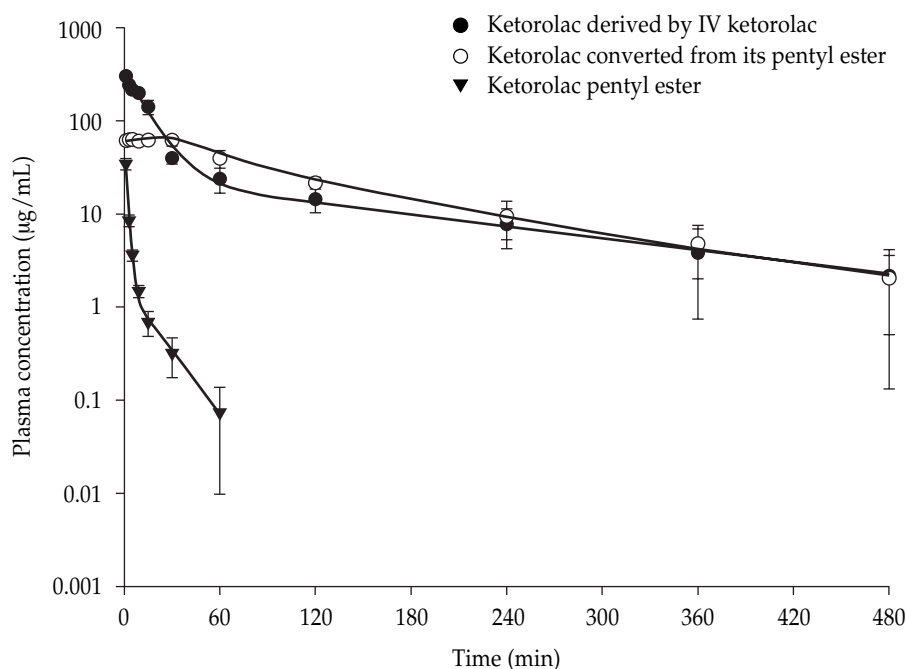
## RESULTS

The pharmacokinetic profiles of ketorolac and its pentyl ester following IV administration of either ketorolac or its pentyl ester are demonstrated in Figure 2 and the Table. Following IV administration of ketorolac, the plasma concentrations of ketorolac were successfully fitted to a two-compartment

model with one distribution phase and one elimination phase (Figure 2 and the Table). Following IV administration of ketorolac pentyl ester, the plasma concentrations of ketorolac pentyl ester declined rapidly and were successfully fitted to a two-compartment model with one distribution phase and one elimination phase. Meanwhile, the conversion of ketorolac pentyl ester to ketorolac occurred rapidly, following the administration of its pentyl ester and the plasma concentrations of ketorolac, which were also fitted to a two-compartment absorption model (Figure 2 and the Table). After comparing the AUC data of ketorolac following IV ketorolac with those following IV ketorolac pentyl ester, we found that there was no significant difference between these two AUC data (Table). This meant that, following IV administration, ketorolac pentyl ester, which was totally converted to ketorolac, was a prodrug of ketorolac.

## DISCUSSION

Depot formulation with prodrug design is one of the methods used to increase the duration of a drug's action [17–19]. For example, several prodrugs such as haloperidol decanoate, fluphenazine enanthate, estradiol cypionate, and testosterone undecanoate, are synthesized from their active drugs, namely haloperidol, fluphenazine, estradiol, and testosterone, by esterification [19,20]. Esterification of drugs with various fatty acids results in an increase in their



**Figure 2.** Plasma concentration-time profiles of ketorolac and its pentyl ester, following intravenous ketorolac or its pentyl ester in 6 rabbits. Data were mean  $\pm$  SE and were fitted by a computer program of PCNONLIN.

**Table.** Pharmacokinetic parameters of ketorolac and its pentyl ester in rabbits

| Parameter            | Unit        | Ketorolac-direct<br>(mean ± SE) | Ketorolac-converted<br>(mean ± SE) | Ketorolac pentyl ester<br>(mean ± SE) |
|----------------------|-------------|---------------------------------|------------------------------------|---------------------------------------|
| A                    | µg/mL       | 294.0 ± 19.0                    | 0.22 ± 0.12                        | 57.0 ± 13.0                           |
| B                    | µg/mL       | 23.5 ± 9.6                      | 70.8 ± 0.2                         | 1.6 ± 0.3                             |
| C                    | µg/mL       | –                               | 70.6 ± 0.4                         | –                                     |
| α                    | 1/min       | 0.07 ± 0.01                     | 0.07 ± 0.10                        | 0.64 ± 0.08                           |
| β                    | 1/min       | 0.005 ± 0.002                   | 0.008 ± 0.001                      | 0.052 ± 0.005                         |
| Ka                   | 1/min       | –                               | 1.448 ± 0.005                      | –                                     |
| T <sub>1/2(α)</sub>  | min         | 9.40 ± 1.30                     | 10.00 ± 14.40                      | 1.08 ± 0.13                           |
| T <sub>1/2(β)</sub>  | min         | 143.0 ± 54.0                    | 87.9 ± 0.2                         | 13.2 ± 1.2                            |
| T <sub>1/2(ka)</sub> | min         | –                               | 0.487 ± 0.002                      | –                                     |
| AUC <sub>0-∞</sub>   | µg • min/mL | 8840 ± 1040                     | 8930 ± 10                          | 119 ± 13                              |
| Cl <sub>t</sub>      | mL/min/kg   | 0.770 ± 0.090                   | 0.968 ± 0.001                      | 72,600 ± 7,800                        |

Equation for ketorolac-direct and its pentyl ester: plasma concentration ( $C_p$ ) =  $Ae^{-\alpha t} + Be^{-\beta t}$ ; equation for ketorolac-converted: plasma concentration ( $C_p$ ) =  $Ae^{-\alpha t} + Be^{-\beta t} - Ce^{-ka t}$ ; A, B, C = intercepts;  $\alpha$  and  $\beta$  are the first-order rate constants for central and tissue compartments, whereas ka is the absorption rate constant; T<sub>1/2</sub> = half-life of the first-order rate constant; AUC<sub>0-∞</sub> = area under the time-concentration graph to time infinity; Cl<sub>t</sub> = total plasma clearance.

Ketorolac-direct: ketorolac which was obtained by direct intravenous injection.

Ketorolac-converted: ketorolac which was converted from ketorolac pentyl ester.

There was no significant difference in AUC data between ketorolac-direct and ketorolac-converted by using two one-sided *t* tests.

lipophilicity [17–19]. When these prodrug-type esters are dissolved in injectable oils and given IM, long durations of actions will be obtained due to a slow-release characteristic of these esters from the oily vehicles [19]. Once released from the vehicles within the muscle, esters will be hydrolyzed by esterases and become the active drugs [17–21]. Esterases exist in many tissues and organs, such as in the blood, brain, liver, lung, etc.

In a previous study, ketorolac pentyl ester was synthesized and formulated into the injectable sesame oil as the oil solution. Following IM injection in rats, a long-acting analgesic effect was found [14]. Since long-acting analgesic is particularly valuable for patients with long-lasting pain, the development of a long-acting NSAID is worth pursuing. In this novel depot, ketorolac pentyl ester was synthesized through a prodrug design with an esterification method [14]. It was expected to be a prodrug of ketorolac *in vivo*. However, this was not tested before.

Following IV administration, the plasma concentrations of ketorolac pentyl ester were successfully fitted to a two-compartment open model with one distribution phase and one elimination phase. The distribution and elimination half-lives were 1.08 ± 0.13 and 13.2 ± 1.2 minutes, respectively (Table). The very short elimination half-life indicated that ketorolac pentyl ester was eliminated quickly from the plasma following IV administration. We also found that the formation of ketorolac from ketorolac pentyl

ester occurred rapidly. A high plasma concentration of ketorolac could be detected even at 2 minutes following the administration of ketorolac pentyl ester (Figure 2). The plasma concentrations of ketorolac-converted were successfully fitted to a two-compartment absorption model with an absorption half-life of 0.487 ± 0.002 minutes (Table). The extremely short half-life further indicated that ketorolac pentyl ester was rapidly converted to ketorolac following IV administration. Under an equi-molar basis of drug administration, we further found that the AUC of ketorolac-converted was equal to that of ketorolac by direct IV administration. This meant that ketorolac pentyl ester, which was totally converted to ketorolac, was a prodrug of ketorolac.

In conclusion, an *in vivo* pharmacokinetic study of ketorolac and its pentyl ester in rabbits was carried out. Following IV administration, ketorolac pentyl ester, which was rapidly and totally converted to ketorolac, was a prodrug of ketorolac.

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# Ketorolac酯化衍生物Ketorolac Pentyl Ester 在白兔之藥物動力學

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Ketorolac是一個強效非固醇類抗發炎劑，最近有一個ketorolac的酯化物-戊酯ketorolac (ketorolac pentyl ester)被合成，並且當戊酯ketorolac製成注射型油劑時可有長效的作用。戊酯ketorolac是以前驅藥的設計方式且以酯化方法合成，其被預測在活體使用時應是ketorolac的前驅藥，但這點尚未被證實。本研究的目的為進行一活體動物之藥物動力學實驗來探討戊酯ketorolac是否是ketorolac的前驅藥。本實驗以六隻白兔分別接受靜脈注射各一次等莫耳數的ketorolac及戊酯ketorolac，並偵測其藥物動力學參數。血中之ketorolac及戊酯ketorolac濃度是以高效能液相層析法來偵測。靜脈注射後，戊酯ketorolac的血漿中濃度快速下降而ketorolac被快速生成，並且戊酯ketorolac會完全轉換成ketorolac。本實驗證實在活體狀態下戊酯ketorolac是ketorolac的前驅藥。本實驗之結論如下：在白兔活體藥物動力學實驗中，戊酯ketorolac被證實是ketorolac的前驅藥。

**關鍵詞：**ketorolac，戊酯ketorolac，藥物動力學，前驅藥

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