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Pharmacokinetics and Postoperative Analgesia of Epidural Tramadol: A Prospective, Pilot Study

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ABSTRACT

BACKGROUND: Tramadol, a centrally acting analgesic drug, can be administered via multiple routes and is generally well tolerated.

OBJECTIVE: This study was designed to assess the pharmacokinetics of epidural tramadol administered preoperatively in Japanese patients undergoing upper abdominal surgery.

METHOD: Japanese patients who were scheduled to undergo upper abdominal surgery in The Kitasato Institute Hospital, Tokyo, Japan, were included. Patients received tramadol 2 mg/kg with 5 mL of 1% mepivacaine epidurally 10 minutes before incision. The serum concentration of tramadol was determined by high-performance liquid chromatography for 21 hours after administration. Serum concentration was determined before tramadol administration and 10, 20, 30, and 60 minutes after tramadol administration, first postoperative night, and first postoperative day. Pain score and adverse events (AEs) were assessed at 1, 3, 6, 12, 18, 24, 36, and 48 hours after surgery by patient interview.

RESULTS: Eleven patients were assessed for enrollment. Seven patients (6 men, 1 woman; mean [SD] age, 61.3 [12.6] years; mean [SD] weight, 59.9 [8.9] kg) provided consent and completed the study. The mean (SD) serum C_{max} of tramadol was 1385.5 (390.8) ng/mL, T_{max} was 0.33 (0.22) hour, and terminal elimination half-life ($t_{1/2\beta}$) was 10.5 (2.3) hours. Four patients complained of nausea; however, only 1 patient was administered an antiemetic. No other AEs were reported.

CONCLUSION: This pilot study found that epidural tramadol administered before incision induced a C_{max} within 30 minutes of administration. The drug was detected in serum at ~21 hours after surgery. (*Curr Ther Res Clin Exp.* 2008;69:49–55)

KEY WORDS: tramadol, pharmacokinetics, epidural.

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INTRODUCTION

Tramadol, a centrally acting analgesic agent with μ-opioid agonist properties, inhibits noradrenaline uptake and causes serotonin release.[1] It can be administered IV, IM, PO, parenterally, and rectally for pain control and is generally well tolerated.[2] Therefore, tramadol might be a useful alternative to opioid analgesics for the treatment of patients with moderately severe, acute, or chronic pain.

Some opioids are administered epidurally with local anesthesia as postoperative analgesia. Several studies have reported that epidural tramadol provided postoperative analgesia and was well tolerated, but pharmacokinetic data of epidural tramadol have not been widely reported.[3–5] One study reported the pharmacokinetics of tramadol administered epidurally in children.[6]

The present study was designed to assess the pharmacokinetics of epidural tramadol administered preoperatively in Japanese patients undergoing upper abdominal surgery.

PATIENTS AND METHODS

PATIENTS

The study was approved by the ethics committee of The Kitasato Institute, Tokyo, Japan. Consecutive Japanese patients who were scheduled to undergo upper abdominal surgery in the Kitasato Institute Hospital were included in this study. They were informed in detail about the purpose of the study and gave written informed consent.

Exclusion criteria included any severe disease complications (eg, abnormal hematology or biochemistry findings), diabetes mellitus, neuropathies, and major surgical procedures.

The anesthetist allocated the patients to treatment. The nurses and pharmacists who measured the patients' pain scores and the surgeons who ordered analgesia for postoperative pain were blinded to the medication administered.

ANESTHESIA REGIMEN

An epidural catheter was inserted between T5 and T10. Ten minutes before incision, tramadol 2 mg/kg with 5 mL of 1% mepivacaine was injected via the epidural catheter. Anesthesia was induced with thiopental sodium or propofol. Tracheal intubation was facilitated with succinylcholine chloride or vecuronium bromide and maintained with oxygen, nitrous oxide, and sevoflurane. After surgery, 0.25% bupivacaine hydrochloride was administered epidurally for 48 hours via an infuser.

BLOOD SAMPLING

Venous blood samples (5 mL) were drawn for analysis of serum tramadol concentration before tramadol administration and 10, 20, 30, and 60 minutes after tramadol administration, immediately after closure, during the first postoperative night, and for 1 postoperative day (mean 21 hours). The samples were centrifuged immediately at 3000 rpm and serum was frozen at –80°C until analysis.

SERUM ANALYSIS

Tramadol hydrochloride was provided by Nippon Shinyaku Company Ltd. (Tokyo, Japan) and metoprolol tartrate as internal standard was from SIGMA (Tokyo, Japan).

The high-performance liquid chromatography system consisted of a model LC-9A constant flow solvent delivery pump, a model SPD-10A vp ultraviolet detector, and a model CTO-10AS vp column oven (Shimadzu Corporation, Kyoto, Japan). The detection wavelength was 225 nm. The analysis and assay of tramadol were performed by warming the reverse-phase column (Mightysil RP-8 GP 150 × 4.6 mm, particle size 5 µm, Kanto Chemical Co., Ltd., Tokyo, Japan) to 40°C. A mixture of 0.1 M phosphate buffer (pH 3.5) and acetonitrile (90:10) was employed as the analytic mobile phase at a flow rate of 1.2 mL/min.

First, 75 µL of metoprolol 10 µg/mL was added to 1.0 mL of serum sample. This solution was stirred in a vortex mixer. The pH was adjusted to 12 with sodium hydroxide 0.1 M. Six milliliters of ethyl acetate were added and then mixed and centrifuged at 3000 rpm for 15 minutes. After the organic phase was transferred to a glass tube, it was evaporated at 40°C. The residue was reconstituted with 200 µL of mobile phase, and 100-µL aliquots were injected after the solution was siphoned through a 0.1-µm filter.[7]

ADVERSE EVENTS

The nurses and pharmacists asked the patients about any adverse events (AEs) when they monitored the patient's pain score. Spontaneously reported AEs were also recorded.

STATISTICAL ANALYSIS

Serum data were analyzed using nonlinear regression analysis. The analysis was performed with PSAG-CP (ASMedica, Osaka, Japan) using a 2-compartment model. Interval data were described as mean (SD).

RESULTS

Eleven patients were assessed for enrollment. Seven patients (6 men, 1 women; mean [SD] age, 61.3 [12.6] years; mean [SD] weight, 59.9 [8.9] kg) provided written consent and were included in the study (**Table I**).

Nonlinear regression analysis gave calibration curves with a correlation coefficient of 0.999 (0.001) (N = 7) for tramadol (0–2000 ng/mL). Tramadol was recovered quantitatively at 93.4%. Assays for within-run and day-to-day reproducibility gave CVs of 9.7% (n = 8) and 1.0% (n = 5), respectively, at concentrations of 500 ng/mL. The detection limit for quantification of this assay method was 5.0 ng/mL.

Mean (SD) serum tramadol concentrations were 0, 1083.8 (472.6), 1278.0 (363.0), 1228.0 (458.1), 770.3 (145.8), 586.0 (107.2), 437.6 (81.5), 347.1 (70.1), and 155.3 (32.3) ng/mL at 0, 0.19, 0.34, 0.5, 1.11, 2.85, 5.67, 10.36, and 21.20 hours after administration, respectively (**Figure**). T_{max} was 0.33 (0.22) hour, C_{max} was 1385.5 (390.8) ng/mL, and terminal elimination half-life ($t_{1/2\beta}$) was 10.5 (2.3) hours (**Table II**).

Four patients complained of nausea; however, only 1 patient was administered an antiemetic. No other AEs were reported.

Table I. Baseline demographic and clinical characteristics in Japanese patients undergoing upper abdominal surgery (N = 7).

Variable	Value
Age, mean (SD), y	61.3 (12.6)
Sex ratio, male/female	6/1
Weight, mean (SD), kg	59.9 (8.9)
Tramadol dose,* mean (SD), mg	119.0 (15.8)
Duration of surgery, mean (SD), h	2.9 (0.6)
Type of surgery, no.	
Total gastrectomy	2
Partial gastrectomy	2
Cholecystectomy	2
Hepatectomy	1

*Dose = 2 mg/kg.

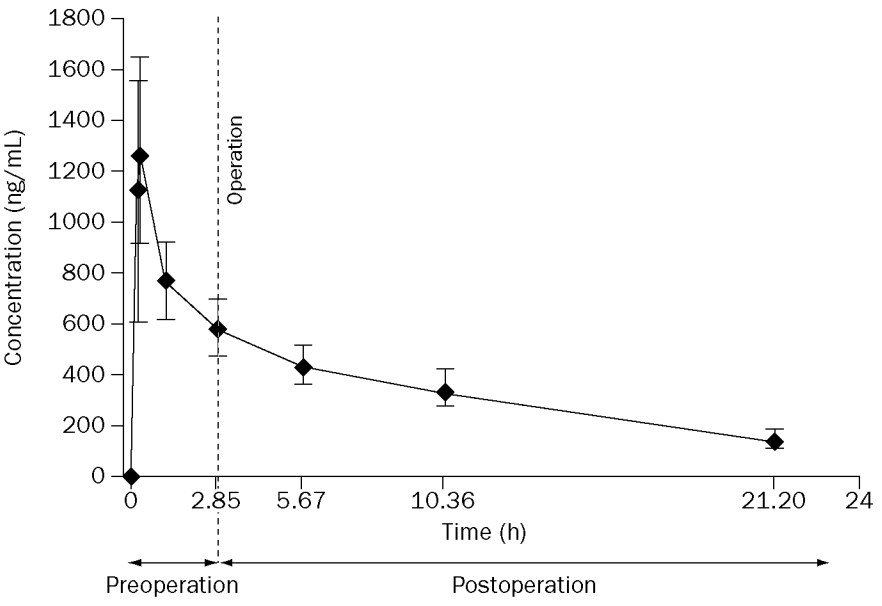

Figure. Mean (SD) serum tramadol concentrations after epidural administration of 2 mg/kg before incision in Japanese patients undergoing upper abdominal surgery (N = 7).

Table II. The pharmacokinetic parameters of tramadol in Japanese patients undergoing upper abdominal surgery (N = 7). Data are mean (SD).

Parameter	Value
$AUC_{0-\infty}$, ng/mL · h^{-1}	10322.8 (1801.6)
C_{max}, ng/mL	1385.5 (390.8)
T_{max}, h	0.33 (0.22)
$t_{1/2\alpha}$, h	0.30 (0.12)
$t_{1/2\beta}$, h	10.5 (2.3)
K_{el}, h^{-1}	0.24 (0.12)

$AUC_{0-\infty}$ = area under the blood concentration–time curve from 0 to infinity; $t_{1/2\alpha}$ = initial decay half-life; $t_{1/2\beta}$ = terminal elimination half-life; K_{el} = elimination rate.

DISCUSSION

In a study of men and dogs by Naraba et al,[8] serum tramadol concentrations were reported to be 1040 and 860 ng/mL, respectively, at 30 minutes after administration. The serum concentrations decreased gradually when 2 healthy volunteers were administered tramadol 100 mg (1.65 mg/kg) IM. In a study by Lintz et al,[9] mean (SD) C_{max} was 308 (89) ng/mL, T_{max} was 1.20 (0.39) hours, and $t_{1/2\beta}$ was 5.5 (0.9) hours when tramadol 100 mg was administered PO to 8 healthy volunteers. A second study by Lintz et al[10] found C_{max} was 422 to 718 ng/mL, T_{max} was 0.25 to 1.00 hours, and $t_{1/2\beta}$ was 5.2 hours when tramadol 100 mg was administered IV to 8 normal volunteers.

Baraka et al[4] reported that epidural tramadol or morphine could be used to provide prolonged postoperative analgesia, and tramadol was well tolerated.[11] Epidural tramadol has been evaluated as a postoperative analgesic since 1991, but there have been few reports on the pharmacokinetics of tramadol. Shimizu et al[11] reported that the analgesic effect was not sufficient when 1 mg/kg of tramadol was administered epidurally. Thus, 2 mg/kg of epidural tramadol was administered to patients undergoing upper abdominal surgery in this study, and the pharmacokinetics of tramadol were evaluated.

In this study, epidural administration of tramadol 2 mg/kg before incision was associated with a mean (SD) peak serum tramadol concentration of 1385.5 (390.8) ng/mL within 30 minutes. The mean (SD) $t_{1/2\beta}$ was 10.5 (2.3) hours, and some serum concentrations remained until ~21 hours after administration. C_{max} was numerically higher, and $t_{1/2}$ appeared longer than those observed with other routes of administration.[8–10] The action of tramadol is thought to be at the spinal level, similar to other opiates (eg, morphine). Tramadol is absorbed immediately into the epidural veniplex after epidural administration because tramadol has a high tissue affinity[12] and is distributed to serum. The minimum effective tramadol serum concentration for postoperative analgesia is not known. However, Lehmann et al[13] suggested that serum tramadol concentrations >300 ng/mL seem necessary to reach the therapeutic window for analgesia. The serum concentration of tramadol was maintained at about one tenth of the

peak serum concentration, between 109.1 and 213.0 ng/mL, up to 21 hours after surgery in this study. This suggests that tramadol continued to be distributed to the serum from the epidural veniplex.

Tramadol is metabolized by cytochrome P450 2D6 (CYP2D6) or sparteine oxygenase to 11 metabolites.[14] The *O*-desmethyl metabolite (M1) of tramadol has 2 to 4 times the analgesic potency than the parent compound, and 4 to 200 times greater affinity for the μ-receptor than the parent compound.[2] Additionally, the (+) enantiomer of tramadol and its metabolites bind more strongly to the μ-receptor than the (-) enantiomer. The mean elimination half-life of tramadol reported after PO or IV administration is 5 to 6 hours in healthy volunteers.[2] Approximately 30% of tramadol is excreted in the urine as an unchanged form and ~60% is excreted as metabolites.[1] One third of the dose is metabolized to the *O*-desmethyl metabolite (+) and (-) M1 by CYP2D6.[15] This enzyme has genetic polymorphism. Therefore, it is important to discuss the pharmacokinetics of the active metabolites and the enantiomers of tramadol in the future. We should also investigate the influence of the CYP2D6 genotype. Additionally, we should evaluate the efficacy and safety of tramadol administered epidurally before incision.

CONCLUSION

This pilot study found that epidural tramadol administered before incision induced a C_{max} within 30 minutes of administration. The drug was detected in serum at ~21 hours after surgery.

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