[Short Communication]

A Novel Method for Determination of Tapentadol in the Serum of Cancer Patients by High-performance Liquid Chromatography with Electrochemical Detection

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(Accepted September 15, 2018)

Abstract: The first clinical use of oral tapentadol tablets in Japan was in August 2014. Tapentadol is mostly metabolized in the liver and has no active metabolites. Therefore, in patients with liver dysfunction, the blood concentration of tapentadol is expected to increase; however, the detailed pharmacokinetics of tapentadol have rarely been investigated. Therefore, a simple and accurate method to measure the blood concentration of tapentadol was developed using HPLC (High performance liquid chromatography) / ECD (electrochemical detector). The mobile phase was 10 mM Na_2HPO_4/CH_3CN (3:1). The column used was the XTerra® RP18, and the voltage of the ECD was set between 300 and 800 mV. The calibration curve was linear in the range of 10 ng/mL to 100 ng/mL ($y = 18544x + 2780.4$, $r = 0.9998$). The intra- and inter-day coefficients of variation were <5.1% and <5.1%, respectively. Therefore, this method was considered to be useful for the measurement of blood concentration of tapentadol in patients with cancer. Using this method, the blood concentration of tapentadol was measured over time in a patient with cancer-associated pain who was treated with tapentadol. The estimated clearance (CL/F) and distribution volume (Vd/F) of tapentadol were 30.4 L/h and 178 L, respectively.

Key words: tapentadol, HPLC, cancer pain

INTRODUCTION

The clinical use of oral tapentadol tablets in Japan was initiated in August 2014. Tapentadol is an analgesic that combines opioid receptor activity and noradrenaline reuptake inhibitory action.[1)] In Phase III clinical trials, it was as effective as morphine and oxycodone for the treatment of moderate to advanced cancer pain and was well tolerated.[2–4)] Tapentadol is mostly metabolized in the liver and has no active metabolites. Therefore, in patients with liver dysfunction, the blood concentration of tapentadol is expected to increase; however, the detailed pharmacokinetics of tapentadol have rarely been investigated. There is an upper limit to the dose of tapentadol owing to the noradrenaline reuptake inhibitory action and it is therefore necessary to determine the pharmacokinetics of tapentadol in actual clinical practice. Currently, there is no simple method for the rapid measurement of the blood concentration using high performance liquid chromatography (HPLC) coupled with an electrochemical detector (ECD). Therefore, we have reported a simple method to measure the blood concentration of tapentadol using HPLC/ECD. We have also reported the pharmacokinetic analysis of tapentadol in a patient with cancer prescribed tapentadol to alleviate pain.

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EXPERIMENT

1. Chemicals

Tapentadol HCl (Lot 1665.1B1.1) was obtained from Janssen Pharmaceutical K.K. The solvents used for the mobile phase were of chromatographic grade. All other chemicals used were of special reagent grade.

2. HPLC/ECD

Chromatograms were obtained using a PU-2080 pump (Nihon Bunko) equipped with an ECD, Coulochem III, and Analytical Cell 5010 (Nippon Dionex). The column used was an XTerra® RP18 (5 μm, 4.6 mm × 50 mm i.d., Waters, Japan) at a temperature of 40℃. The separation of tapentadol and the interference in serum were achieved using a mobile phase of 10 mM Na_2HPO_4/CH_3CN (3:1) at a flow rate of 1.0 mL/min. The voltage of the ECD was set between 300 and 800 mV. Data analysis was performed using ChromNAV 1.17 (Nihon Bunko).

3. Extraction procedure

Serum samples (1.0 mL) were added to 0.5 mL 4 N NaOH and then extracted using 5 mL dichloromethane/diethyl ether (1:1). The samples were mixed, centrifuged for 10 min at 3,000 rpm, and the supernatant containing dichloromethane/diethyl ether (top layer) was transferred to a clean tube. The top layer was then evaporated to dryness. The dried residue was dissolved in 200 μL of the mobile phase, and 40 μL of this solution was injected into the HPLC system.

4. HPLC/ECD assay validation

The linearity over the measurement range was assessed by comparison with standard curves in the range of 10–100 ng/mL (10, 25, 50, and 100 ng/mL) using human serum, and the samples were analyzed using the described HPLC/ECD method. The intra-day (n = 10) and inter-day (n = 5) reproducibility values were determined by replicate analysis of the tapentadol samples at high (100 ng/mL) and low (10 ng/mL) concentrations. The extraction rate was calculated based on the absolute calibration curve.

5. Determination of tapentadol in patient serum

A patient with cancer admitted to Kitasato University Hospital and orally administered tapentadol (Tapenta® Tablets; Janssen Pharmaceutical K.K.) was tested after obtaining written informed consent for blood sampling. Blood samples of obtained the steady state before administration, and were obtained at 5 h and 10 h after administration. The pharmacokinetic parameters of serum tapentadol were estimated using a one-compartment model with first-order absorption; subsequent analysis was performed using the software WinNonlin® (Ver 6.4, Pharsight Corporation, CA, USA). For calculation of pharmacokinetic parameters, an optimal error model was determined from the additive model, the exponential model, and the mixed model. The measurement of serum tapentadol concentrations was approved by the ethics committee of Kitasato University Hospital.

RESULTS

1. Chromatographic separation and quantitative response

In the optimal voltage test, the highest peak for tapentadol was obtained at 800 mV, and the lowest peak was obtained at 300 mV. Therefore, the voltage of the working electrode of the ECD was set between 300 and 800 mV.

The tapentadol peak was detected within 4.7 min and was well separated from the serum component (Fig. 1). The recovery rate was 81.6%. A linear regression analysis of the standard curve in the range of 10–100 ng/mL yielded the following equation: $y = 18544x + 2780.4$, $r = 0.9998$ (Fig. 2). The lower limit of quantification was 1.0 ng/mL (S/N = 3). The intra- and inter-day coefficients of variation were <5.1% and <5.1%, respectively (Table 1).

2. Determination of tapentadol in patient serum

This analytical method was applied to determine the serum concentrations of tapentadol in a patient with

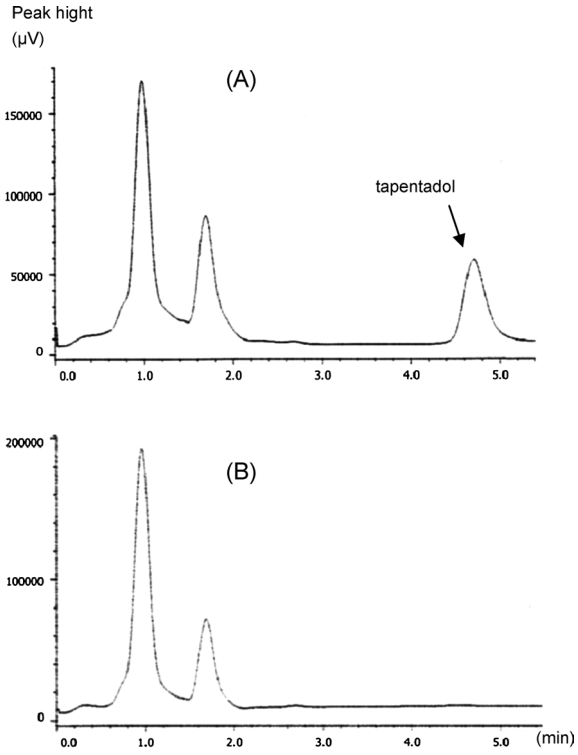

Fig. 1 Chromatograms of tapentadol (A) and control (B) in human serum.

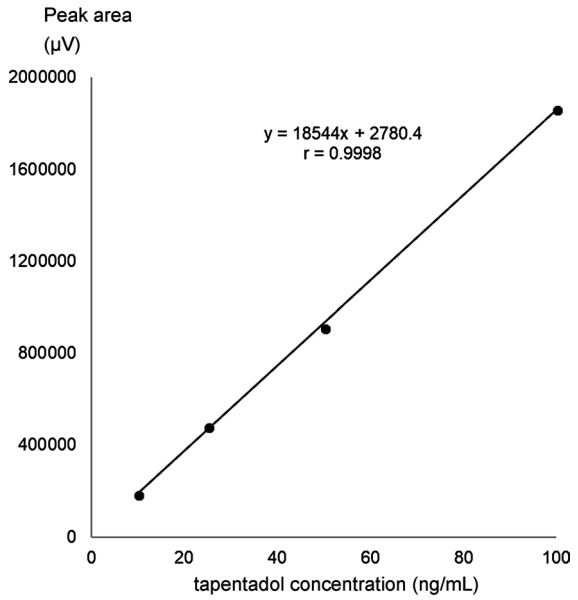

Fig. 2 Calibration curve of tapentadol.

Table 1 Reproducibility of the analyses

Concentration (ng/mL)	Intra-day C.V.% (n = 10)	Inter-day C.V.% (n = 5)
10	2.5	5.1
100	5.1	3.1

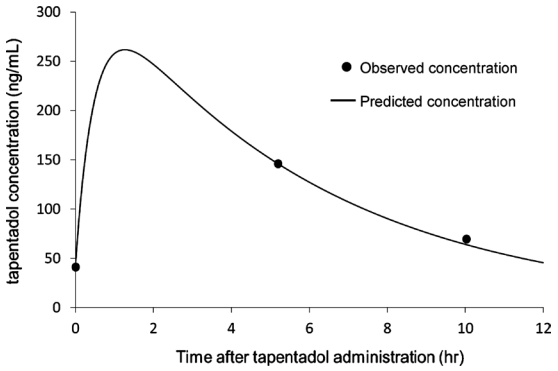

Fig. 3 Observed blood concentration and predictive blood concentration simulation of tapentadol (100 mg/day) in a cancer pain patient.

cancer-associated pain. This patient was a 44-year-old male, body weight 95.5 kg, and was abnormal as T-Bil; 1.2 mg/dL, Scr; 1.4 mg/dL. Tapentadol was administered 50 mg twice a day and blood was collected on day 3 after administration. The following tapentadol blood concentrations were measured: 40.8 ng/mL before administration; 145.2 ng/mL at 5 h after administration; and 68.8 ng/mL at 10 h after administration. The estimated clearance (CL/F) and distribution volume (Vd/F) of tapentadol were 30.4 L/h and 178 L, respectively. The measured blood concentration and simulated predicted blood concentration of tapentadol in a patient with cancer pain are shown in Fig. 3.

DISCUSSION

Several studies have reported the measurement of the blood concentration of tapentadol using HPLC-FL (spectrofluorimetric detection)[5] and LC-MS/MS method.[6, 7] We aimed to develop a simple and clinically useful method to measure the blood concentration of tapentadol using HPLC/ECD. By HPLC/FL,[5] tapentadol was measurable to 0.3 ng/mL; and by LC/MS/MS,[6] tapentadol was measurable to 0.2 ng/mL. Our HPLC/ECD method has a limit of quantification of 1.0 ng/mL, which was less sensitive than existing methods, but is a clinically relevant concentration. In addition, the extraction method is simple and the peak of tapentadol is detected in 4.7 min, so it can be measured in a short time. Furthermore, it is the first reported method using HPLC/ECD.

The blood concentration of tapentadol was measured over time in a patient with cancer-associated pain who was treated with tapentadol. The pharmacokinetic parameters of tapentadol extended-release tablets in healthy adult males were previously reported as: CL/F, 92–96 L/h; Vd/F, 471–540 L.[8]

These were lower than the parameters measured in our study; this may be due to differences in bioavailability. In addition, as the values of T-Bil (total bilirubin) and SCr (serum creatinine) were 1.2 mg/dL and 1.4 mg/dL, respectively, for this patient, it was thought that CL/F was low owing to the occurrence of renal dysfunction and mild liver dysfunction.

We plan to increase the number of cases in future studies and analyze the population pharmacokinetics of tapentadol in patients with cancer pain.

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