Pharmacokinetic Analysis, Analgesic Effects, and Adverse Effects of Tapentadol in Cancer Patients with Pain

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Received January 27, 2020; accepted March 21, 2020

In this study, we conducted a pharmacokinetic analysis of tapentadol (TP) in Japanese patients with cancer pain and identified covariates influencing pharmacokinetic parameters. In addition, the analgesic effects and adverse effects of TP were investigated. Data were collected from in-patients with cancer pain who had been administered TP as an extended-release formula. The median (range) estimated clearance (CL/F) and distribution volume (Vd/F) of TP were 86.7 (31.3–213.7) L/h and 1288 (189–6736) L, respectively. There was a strong negative correlation between CL/F and age, Child–Pugh score, and albumin-bilirubin (ALBI) score. The subjects were further divided into two groups according to the factors highly correlated with CL/F. The CL/F of patients in the Child–Pugh B group was 0.46-times that of patients in the Child–Pugh A group. In addition, the CL/F of patients with an ALBI score ≥−2.40 was 0.56-times that of patients with ALBI scores ≤−2.40, and both differences were statistically significant (p < 0.05). The mean intensity of pain over 24 h was investigated daily from before starting TP for the first 7 d of the treatment. TP reduced pain in six of nine patients; the mean pain visual analogue scale score decreased significantly from 59.2 mm before administration to 42.5 mm at days 5–7. Overall, the Child–Pugh and ALBI scores significantly affected the clearance of TP, which was reduced in patients with impaired liver function. These results suggest that TP is an opioid with a sufficient analgesic effect for cancer patients.

Key words tapentadol; pharmacokinetic analysis; cancer pain; covariate; liver function

INTRODUCTION

Tapentadol (TP) is a centrally acting analgesic with two mechanisms of action: μ-opioid receptor agonism (MOR) and noradrenaline reuptake inhibition (NAI). In phase III clinical trials,1,2) TP was shown to have comparable effectiveness to morphine or oxycodone for the treatment of moderate to severe cancer pain and was well-tolerated. In addition, the incidence of gastrointestinal disorders, such as constipation and nausea, which are characteristic adverse effects of opioid analgesics, tended to be lower than that of morphine or oxycodone.3) The elimination half-life of TP in the serum of healthy male Caucasians was estimated at approximately 4 h, and the absolute bioavailability of the TP immediate-release formulation was 32% when administered orally under fasting conditions.4) The major pathway of TP metabolism is conjugation with glucuronic acid. Only 3% of the dose was eliminated in the form of unchanged TP, with almost the entire dose (96%) metabolized to inactive conjugates,5) indicating that renal dysfunction would have a negligible effect on TP clearance. A population-scale pharmacokinetics analysis of TP serum concentrations in healthy subjects and non-cancer patients with moderate or severe pain administered the immediate-release formulation identified total bilirubin as a significant covariate affecting TP clearance.6) Another study using the sustained-release TP formulation in healthy subjects and non-cancer pain patients showed that age and aspartate aminotransferase levels were significant covariates moderating TP clearance.7)

As the main metabolic pathway of TP is the liver, the clearance of TP would be expected to be reduced in cancer patients with compromised liver function. However, studies on the pharmacokinetics of TP reported to date were conducted under contexts that vastly differ from the use of TP in Japan in terms of race, disease, and formulation characteristics. Therefore, the aim of the present study was to conduct a pharmacokinetic analysis of TP in Japanese patients with cancer pain and identify the significant covariates affecting TP clearance. We further investigated the analgesic effects and adverse effects of TP in cancer pain patients.

MATERIALS AND METHODS

Subjects and Administration Method This study included cancer pain patients who had been administered the extended-release formula of TP (TAPENTA® Tablets, Janssen Pharmaceutical K.K., Japan) at Kitasato University Hospital between April 2016 and November 2018. The patients were explained the study aims before agreeing to participate and provided written informed consent. Patients receiving combination therapy for the purpose of pain relief, such as surgery...
and nerve block, during the study period and patients judged by doctors to be inappropriate for study participation were excluded. When switching from other opioids, the daily dose of TP was established based on the equivalent ratio of opioids (tramadol oral:oxycodone oral:TP = 7.5:1:5) and was split into two doses administered every 12h. In the case of opioid-naïve patients, TP was initially administered at a dose of 25 mg twice a day and was then increased or decreased as appropriate. This study was approved by the ethics committee of the Department of Medicine, Kitasato University Hospital (B15-137).

**Sampling and Measurement of Serum TP Concentration**

The TP concentration in the serum of patients was determined after at least 48h from starting TP or changing the dose. Blood samples were obtained in the steady-state before administration, and at 5 and 10h after administration of the TP extended-release formulation. After centrifugation (1610×g for 10 min), the supernatant was collected and the TP serum concentration was measured using HPLC-electrochemical detection in accordance with the measurement method of Kokubun et al. Serum samples (1.0 mL) were added to 0.5 mL of 4N NaOH and then extracted using 5 mL dichloromethane:diethyl ether (1:1). The samples were mixed for 10 min, centrifuged for 10 min at 1120 ×g, and the supernatant containing dichloromethane:diethyl ether (top layer) was transferred to a clean tube. The top layer was then evaporated to dryness, and the dried residue was dissolved in 200 µL of the mobile phase, which was used as the measurement sample. TP HCl (Lot 1665.1B1.1) was obtained from Lipomed AG Switzerland. Chromatograms were obtained using a PU-2080 pump (Nihon Bunko, Japan) equipped with a Coulochem III and Analytical Cell 5010 electrochemical detector (Nippon Dionex, Japan). The XTerra RP18 column (5 µm, 4.6 × 50 mm i.d., Waters, Japan) was used at 40°C. The separation of TP and the interferents in serum was achieved using a mobile phase of 10 mM Na2HPO4:CH3CN (3:1) at a flow rate of 1.0 mL/min. The voltage of the electrochemical detector was set between 300 and 800 mV. Data analysis was performed using ChromNAV 1.17 software (Nihon Bunko). The lower limit of quantification was 1.0 ng/mL.

**Individual Pharmacokinetic Analysis**

The pharmacokinetic parameters of serum TP were estimated using a one-

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**Table 1. Patient Characteristics and Laboratory Data**

| Case | Age | Sex | Height (m) | Weight (kg) | Main diagnosis | Previous opioids | TP dose (mg/d) | PS | Alb (mg/dL) | T-Bil (mg/dL) | eGFR (mL/min/1.73 m²) | Child pugh Score | Classification | ALBI grade Score |
|------|-----|-----|------------|-------------|----------------|-----------------|----------------|----|-------------|----------------|-------------------|-----------------|---------------|-----------------|
| 1    | 70  | M   | 1.63       | 49.7        | Esophageal cancer | Oxycodone       | 400            | 1  | 3.6         | 0.5            | 60                | 6               | A              | −2.44           |
| 2    | 62  | M   | 1.56       | 46.5        | Pancreatic body cancer | No previous opioid | 100            | 1  | 4.1         | 0.7            | 88                | 5               | A              | −2.77           |
| 3    | 74  | M   | 1.60       | 47.0        | Small cell lung cancer | Oxycodone       | 400            | 2  | 4.9         | 0.4            | 58                | 5               | A              | −3.61           |
| 4    | 44  | M   | 1.69       | 95.5        | Pancreatic head cancer | Oxycodone       | 100            | 1  | 3.7         | 1.2            | 45                | 6               | A              | −2.28           |
| 5    | 77  | F   | 1.50       | 37.7        | Gall cancer | No previous opioid | 300            | 4  | 2.1         | 0.5            | 42                | 7               | B              | −1.17           |
| 6    | 75  | M   | 1.64       | 62.8        | Pancreatic cancer | No previous opioid | 50             | 1  | 2.6         | 1.7            | 57                | 9               | B              | −1.24           |
| 7    | 63  | M   | 1.66       | 79.4        | Pancreatic body cancer | No previous opioid | 50             | 0  | 4.0         | 0.9            | 74                | 5               | A              | −2.62           |
| 8    | 77  | M   | 1.67       | 52.1        | Pancreatic head cancer | No previous opioid | 50             | 2  | 3.6         | 10.9           | 88                | 8               | B              | −1.56           |
| 9    | 57  | M   | 1.70       | 56.9        | Pancreatic tail cancer | No previous opioid | 50             | 0  | 4.0         | 1.2            | 68                | 5               | A              | −2.53           |
| 10   | 62  | M   | 1.71       | 41.6        | Diffuse large B-cell lymphoma | No previous opioid | 100            | 3  | 3.0         | 0.2            | 116               | 6               | A              | −2.20           |
| 11   | 83  | M   | 1.55       | 56.0        | Swamous cell carcinoma | Tramadol        | 200            | 1  | 2.9         | 0.6            | 85                | 6               | A              | −1.80           |
| 12   | 40  | M   | 1.72       | 55.2        | Pancreatic body cancer | Tramadol        | 250            | 0  | 4.0         | 1.0            | 98                | 5               | A              | −2.59           |
| 13   | 64  | F   | 1.47       | 32.9        | Pancreatic head cancer | Tramadol        | 50             | 1  | 3.6         | 1.3            | 82                | 7               | B              | −2.17           |
| 14   | 53  | F   | 1.53       | 38.6        | Pancreatic body cancer | Tramadol        | 100            | 0  | 4.6         | 0.3            | 63                | 6               | A              | −3.44           |
| 15   | 53  | F   | 1.54       | 46.4        | Rectal cancer | Oxycodone       | 250            | 2  | 2.8         | 0.5            | 90                | 6               | A              | −1.76           |
| 16   | 70  | F   | 1.53       | 59.0        | Left ureteral cancer | No previous opioid | 150            | 2  | 3.1         | 0.5            | 36                | 6               | A              | −2.02           |
| 17   | 45  | F   | 1.62       | 45.3        | Gallbladder neuroendocrine cancer | No previous opioid | 300            | 1  | 2.9         | 2.9            | 112               | 7               | B              | −2.00           |

Median 63  1.62  49.7  100  1  3.6  0.7  74  6  −2.20
Maximum 83  1.72  95.5  400  4  4.9  10.9  116  9  −1.17
Minimum 40  1.47  32.9  50  0  2.1  0.2  36  5  −3.61

M: male, F:female, PS: performance status, alb: albumin, T-bil: total bilirubin, eGFR: estimated glomerular filtration rate.
compartment model with first-order absorption; subsequent analysis was performed using WinNonlin software (Ver 7.0, Pharsight Corporation, CA, U.S.A.). An optimal error model was determined from the additive model, exponential model, and mixed model. The pharmacokinetic parameters included the estimated clearance (CL/F) and distribution volume (Vd/F) of TP. The absorption rate constant (Ka) was fixed at 1.08 based on the report of Zhang et al.9

Covariates Analysis The correlation coefficients were determined between CL/F or Vd/F and age, weight, albumin, total bilirubin (T-Bil), estimated glomerular filtration rate (eGFR), Child–Pugh score,10,11 and albumin-bilirubin (ALBI) score12 using RcmdrPlugin.EZR (version 1.35).13 The ALBI score and eGFR were calculated from the following formulas: ALBI score = 0.66 × log10 T-Bil (µmol/L) + (−0.085) × albumin (g/L) and eGFR = 194 × serum creatinine−1.094 × age−0.287. The Child–Pugh classification was calculated from the following five items: hepatic encephalopathy, ascites, T-Bil, albumin, and prothrombin time/international normalized ratio. Furthermore, the subjects were divided into two groups according to the factors highly correlated with CL/F or Vd/F. According to the correlation analysis, subjects were divided into two groups by age (< 65 years, ≥ 65 years), Child–Pugh classification (A, B), and ALBI score (≤ 2.40, > 2.40), and their CL/F and Vd/F values were compared using the Mann–Whitney U test. A p-value less than 0.05 was considered statistically significant. Classification by age was established at 65 years, which was defined as the cut-off for an elderly or young patient in many developed countries such as Japan.14 The cut-off point for the ALBI score was determined to be −2.40, which was the midpoint of the calculated range (−1.17 to −3.61). Furthermore, the subjects were divided into two groups by these significant covariate factors, and each predicted TP serum concentration curve was drawn.

Analgesic Effects and Adverse Effects The mean intensity of pain, nausea, sleepiness, and constipation over 24 h was investigated daily from before starting TP treatment for 7 d of administration. In addition, the intensity of pain, nausea, sleepiness, and staggering was investigated before treatment (on the day of measurement of serum TP concentration in steady-state) and at 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after administration of the TP extended-release formulation. The intensity was quantified according to the visual analogue scale (VAS), and VAS values were compared using the Wilcoxon rank sum test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics Patient characteristics and laboratory data are shown in Table 1. Data were collected from 17 patients (11 males and 6 females, 47 sampling points). The pre-administration drugs before TP dosing included tramadol in four cases and oxycodone in four cases; the other nine cases were opioid-naive.

Serum TP Concentration and Individual Pharmacokinetic Analysis The observed steady-state TP serum concentrations before administration and at 5 and 10 h into administration, divided by the single dose, are plotted in Fig. 1. TP parameter estimates, including the apparent clearance (CL/F) and distribution volume (Vd/F), from pharmacokinetic modeling are shown in Table 2.

Covariates Analysis The correlation coefficient between CL/F and age, weight, albumin, T-Bil, eGFR, Child–Pugh score, and ALBI score was −0.5146, −0.2645, 0.4836, −0.2904, 0.3935, −0.6216, and −0.5583. Therefore, there were strong negative correlations between CL/F and age, Child–Pugh, and ALBI scores. By contrast, Vd/F was not correlated with any of the covariates. The subjects were then divided into two groups based on the three factors with the highest correlation coefficient (Fig. 2). The CL/F of the Child–Pugh B group was 0.46-times that of the Child–Pugh A group (p = 0.0185), the CL/F of the ALBI >−2.40 group was

Table 2. TP Parameter Estimates from Pharmacokinetic Modeling

|            | CL/F (L/h) | Vd/F (L) |
|------------|------------|----------|
| 1          | 64.5       | 899      |
| 2          | 162.5      | 1645     |
| 3          | 116.7      | 820      |
| 4          | 31.3       | 189      |
| 5          | 39.4       | 664      |
| 6          | 49.4       | 1288     |
| 7          | 86.7       | 3667     |
| 8          | 47.4       | 1801     |
| 9          | 140.8      | 971      |
| 10         | 86.7       | 1210     |
| 11         | 78.6       | 495      |
| 12         | 213.7      | 2072     |
| 13         | 78.0       | 595      |
| 14         | 151.9      | 1592     |
| 15         | 145.1      | 1443     |
| 16         | 97.7       | 1709     |
| 17         | 96.7       | 6736     |

Median 86.7 1288
Maximum 213.7 6736
Minimum 31.3 189

CL/F: apparent clearance Vd/F: apparent volume of distribution.
0.56-times that of the ALBI \( \leq -2.40 \) group (\( p = 0.0365 \)), and the \( CL/F \) of the \( >65 \) years of age group tended to be lower than that of the under 65 group, but the difference was not statistically significant.

Furthermore, the steady-state TP serum concentration measured before to 12 h after administration at 25 mg per dose was simulated based on the calculated mean \( CL/F \) of the Child–Pugh A, Child–Pugh B, ALBI score \( \leq -2.40 \), and ALBI score \( >-2.40 \) groups (fixed \( K_a = 1.08/\text{h}, V_d = 1288\text{L} \)), as shown in Fig. 3. TP serum concentration profile of Child–Pugh B, ALBI score \( >-2.40 \) groups was higher than Child–Pugh A, ALBI score \( \leq -2.40 \) groups.

**Analgesic Effects and Adverse Effects** The intensities of the transition of pain, nausea, sleepiness, and constipation before TP administration until the 7th day of administration are shown in Fig. 4, as measured according to the VAS. The intensity of pain could be evaluated in nine patients, and the intensity of nausea, sleepiness, and constipation could be evaluated in four patients. TP reduced pain in six of the nine patients, with a significant decrease in the mean VAS.
from 59.2 mm before administration to 42.5 mm on days 5–7. Nausea and sleepiness did not change significantly after TP administration. Constipation was relieved in two cases of switching from oxycodone to TP, whereas the VAS for constipation increased in the two opioid-naïve cases.

Figure 5 shows the steady-state change in serum TP concentration with respect to the transition intensity of pain, nausea, sleepiness, and staggering before administration, and for the first 12 h after TP administration. Although there were cases in which the VAS fluctuated, there was no association with changes in serum TP concentration. Overall, the mean VAS did not change substantially for all cases, and there was no relationship between the transition in TP serum concentrations and analgesic or adverse effects.

DISCUSSION

This is the first analysis of the pharmacokinetics and analgesic and adverse effects of TP in Japanese patients with cancer pain. The pharmacokinetic parameters calculated in this study (\(CL/F\) of 86.7 L/h and \(V_d/F\) of 1288 L) are similar to those reported by Zhang et al.\(^9\) who conducted a population-level pharmacokinetic analysis of TP in Japanese subjects (\(CL/F\) of 143 L/h and \(V_d/F\) of 1270 L), which is attributed to the same ethnic background and TP preparation. The higher \(CL/F\) obtained in the previous study is considered to reflect the fact that non-cancer patients were the subjects.

The Child–Pugh score is a widely used objective and standard method for evaluating liver function in patients with hepatocellular carcinoma, and the ALBI score is an objective measure for evaluating liver function based on albumin and T-Bil levels. Based on both of these measures, the clearance of TP in patients with impaired liver function was found to be reduced. The major pathway of TP metabolism is conjugation with glucuronic acid, and 96% of the administered dose is eliminated in the form of inactive conjugates; therefore, hepatic function appears to strongly affect TP clearance. Zhang et al.\(^9\) estimated liver function based on albumin and alanine transaminase levels, and found that albumin was a significant covariate of clearance, which is line with the results of the present study.

Owing to the relatively small sample size, we divided the patients into two groups according to age as well as Child–Pugh and ALBI score for comparison. Inclusion of more cases might help to determine a clearer cut-off value for evaluation. Age and the Child–Pugh and ALBI scores are measured on an ordinal scale; therefore, we consider that the cut-off values that we adopted may be not be relevant in clinical practice.
However, the finding of reduced clearance of TP in the impaired liver function group based on the Child–Pugh and ALBI scores highlights the importance of paying attention to the occurrence of adverse events such as sleepiness, nausea, and staggering for adjusting the TP dose. Moreover, both the previous study and present study demonstrated no correlation between TP clearance and renal function.

Evaluation of the intensity of pain, nausea, sleepiness, and constipation during the 8 d from before the start of TP administration until the 7th day showed that TP improved pain in the majority of patients, and the mean VAS also decreased significantly after the start of TP. By contrast, TP did not have a major effect on nausea and sleepiness, and the mean VAS of constipation after the start of TP actually decreased. As TP exerts an analgesic effect in combination with MOR and NAI, it is considered to have a sufficient analgesic effect despite its lower affinity to MOR than that of morphine, and there are few adverse effects related to MOR. In this study, constipation improved in two cases of switching from oxycodone to TP, further supporting that this adverse effect is reduced with TP compared to other strong opioids. The lack of association between analgesic effects or adverse events and changes in serum TP concentration in each case may be related to the influence of several factors such as body movements and meals. Breakthrough pain may also occur without a pain trigger. In addition, the lack of association between the mean VAS and serum TP concentration suggests that daily fluctuations in serum TP concentration when taking TP sustained-release tablets are minimal and would not affect the analgesic or adverse events.

Overall, this study indicates that the Child–Pugh and ALBI scores are the main factors that significantly affect the clearance of TP in cancer patients with pain, and clearance is reduced in patients with impaired liver function. In addition, TP has less of an adverse effect of constipation than other strong opioids. Thus, TP appears to be an opioid with a sufficient analgesic effect.

Acknowledgments Editorial support for the writing of this manuscript was provided by gastroenterologists and anesthesiologists at Kitasato University Hospital. The authors would like to thank all participating patients and the medical doctors and nurses of the participating institutions for their contributions to data collection.

Conflict of Interest The authors declare no conflict of interest.

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