Individual Variations in the Elimination Process of Fentanyl in Patients

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Summary: The quantitative determination of serum fentanyl (FT), urinary FT and its main metabolite, Nor-FT was examined to ascertain the individual variation in the elimination process of FT among 17 patients. The pharmacokinetics of FT was solved from the obtained data using 2-compartment model including the metabolic process. Furthermore, we compared Nor-FT excretion with CYP3A4 activity based on urinary 6β-hydroxycortisol (6β-OHF) and cortisol (F) excretion ratio.

FT and Nor-FT were determined by isotope dilution analysis using deuterium labeled FT (FT-2H19) or Nor-FT (Nor-FT-2H10) as internal standards. The isotopic fractionation was achieved by a capillary gas chromatograph equipped with a surface ionization detector. The pharmacokinetic parameters were calculated from serum FT concentration time profiles and excreted amount of FT and Nor-FT in urine, using the pharmacokinetic data analysis software, WinNonlin standard Ver. 1.5 (Scientific Consulting). Urinary F and 6β-OHF concentrations were determined by HPLC using fludrocortisone as an internal standard after conversion to fluorescence derivative using 1,2-diamino-4,5-methylenedioxybenzene.

The obtained pharmacokinetic parameters showed considerable difference between individuals. The predicted time course for FT and Nor-FT was adapted to FT kinetics. The predicted final excretion rates of FT and Nor-FT were 0.14-15.77% (mean 4.30%) and 7.36-99.38% (mean 55.12%), respectively. The CYP3A4 activity obtained from steroid excretion was not reflected by FT elimination in this study for a low dose of FT (5 μg/kg).

Key words: Fentanyl, Isotopic fractionation, Deuterium analogue, Pharmacokinetics, 2-compartment model, Metabolism, CYP3A4

Introduction

Fentanyl [1-(2-phenethyl)-4-N-(N-propionylanilino) piperidine, FT] is a synthetic narcotic analgesic, it has a more effective and a shorter half-life than morphine. It causes respiratory depression and its efficacy attenuates rapidly1). Therefore, many pharmacokinetics studies have reported use of administration schedules of FT.

For the analysis of FT in plasma or serum, radioimmunoassay (RIA)2,3), high-performance liquid chromatography (HPLC)4,6>, and gas chromatography (GC)3,6,7) have been used. Several pharmacokinetic studies of FT have previously reported determinations using some of these methods, however, discordance of pharmacokinetic parameters between these reports has been reported8). Woestenborghs et al9), reported that the discordance was due to a lack of reproducibility of determination limit, and an accurate assay method for these levels is necessary for study of the pharmacokinetics of FT.

Isotope dilution analysis is precise and reproducible, because an isotope labeled compound is similar to the unlabeled compound during the extraction, concentration, and derivation procedures. We have reported isotope dilution analysis for serum FT in patients by isotopic fractionation of FT from its deuterated analogues using capillary GC9). Furthermore, we demonstrated that this technique could be applied to determine urinary FT and its main metabolite, Nor–FT10).

In the present study, we examined quantitative determination of serum FT, urinary FT and urinary Nor–FT after conversion to its methyl derivative, Nor–FT–Me, to ascertain the individual variations of serum level or the elimination of FT or Nor–FT in patients. Furthermore, the pharmacokinetics of FT was solved from the obtained data using a 2-compartment model including the metabolic process. We also examined the influence of the main metabolizing enzyme for FT, CYP3A4, on FT elimination.

Experimental

Collection of Serum and Urine Samples

The subjects of the study (Table I) were 17 surgical patients, 12 women, and 5 men, ranging in age from 33 to 71 years. None of the patients had metabolic disease.
Informed consent was given by all patients, and the project was approved by the Research Committee of the Hospital.

Anesthesia was induced by thiamylal (3 mg/kg) i.v. and vecuronium bromide (0.1 mg/kg) i.v. FT was administered i.v. (5 µg/kg) by a bolus injection as fentanyl citrate (Fentanest, Sankyo) for introduction of anesthesia. Anesthesia was maintained by inhalation of isoflurane or sevoflurane.

Blood samples were collected 12 times up to 3 hr after FT administration. These times were 0 (before administration), 1, 6, 11, 16, 21, 31, 61, 91, 121, 151, and 181 min after administration. The blood was drawn from the cubitus vein and the collection volume was 3 ml. The indwelling needle was Teflon coated and contained physiological saline. The collected blood sample was transferred to an Insepack-S (Sekisui Medical) tube, kept at 37°C for 30 min, centrifuged for 3000 rpm/5 min, and the serum was separated. The serum (1.5 ml) was put into a silanized tube, capped, sealed with Parafilm, and refrigerated for 5–9 days at 4°C until analysis.

Urine samples were collected 7 times up to 8 hr after FT administration by exchange of plastic bag via a catheter. Collected urine samples were transferred to silanized tubes, capped, sealed with Parafilm, and stored for 9–15 days at 4°C until analysis.

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<th>Weight (kg)</th>
<th>BMI</th>
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Urine samples were collected 7 times up to 8 hr after FT administration by exchange of plastic bag via a catheter. Collected urine samples were transferred to silanized tubes, capped, sealed with Parafilm, and stored for 9–15 days at 4°C until analysis.

**Determination Procedure of FT or Nor-FT**

FT, 1-nonadeuterophenethyl-4-N-pentadeuteropropionyl-pentadeutero anilino-piperidine (FT-2H19), N-propionyl-anilinopiperidine (Nor-FT) and N-pentadeuteropropionyl-pentadeuteroanilino-piperidine (Nor-FT-3H10) were prepared as described previously. The chemical structures of FT, Nor-FT and its deuterated analogues are shown in Fig. 1.

Serum samples were prepared by the previously described extraction method with 1.5 ml of serum, to which was added 20 ng of FT-2H19 as an internal standard. The urine samples for FT were prepared by the previously described extraction method with 1 ml of urine, to which was added 20 ng of FT-2H19 as internal standard. Urine samples for Nor-FT were prepared by...
the previously described extraction and methyl derivation procedure\(^1\) with 1 ml of urine, to which was added 200 ng of Nor–FT–\(^2\)H\(_{10}\) as an internal standard. The FT or Nor–FT concentration in each sample was calculated from the peak area ratio (FT or Nor–FT/IS) by capillary GC.

The GC system was equipped with a fused-silica capillary column (25 m, 0.22 mm i.d.) with chemically bonded methylpolysiloxane and a film thickness of 0.25 mm (Hicap–CBP1–M25–025, Shimadzu). A Shimadzu model GC–14A gas chromatograph equipped with a surface ionization detector (SID) was used. The inlet system used was solvent less of moving-needle type. The peak area was measured by a data processor, Shimadzu model C-R5A Chromatopac. The injection port was kept at 290°C, the column was operated at 180°C for Nor–FT or 260°C for FT and the detector temperature was 320°C. The carrier gas was helium at 1.4 ml/min.

### Calculation of Pharmacokinetic Parameters

The pharmacokinetic model of FT with a bolus of dosage \(D\) is shown in Fig. 2. In this model, \(A\) and \(B\) are the amounts of FT in the central and peripheral compartments, respectively. \(U\) is the cumulative excretion amount of FT in urine. \(N\) is the amount of Nor–FT formed from FT in the body. \(E\) is the amount of another metabolite formed from FT. \(M\) is the cumulative excretion amount of Nor–FT in urine. \(k_{12}\) is the distribution rate constant of FT form central to peripheral, and \(k_{21}\) is the reverse. \(k_{10}\) is the excretion rate constant of FT to urine. \(k_m\) is the elimination rate constant of FT by the metabolism, and \(F_e\) is the fraction of Nor–FT. \(k_u\) is the excretion rate constant of Nor–FT to urine. \(T_1\) and \(T_2\) are the respective lag times of FT and Nor–FT until excretion to urine.

Differential equations concerning \(A, B, U, M,\) and \(C\) as serum concentration of FT can be converted to integral equations as described below by Laplace transformation.

\[
C = \frac{D}{(\alpha - \beta) \cdot V_c} \left( (\alpha - k_{21}) e^{-\alpha t} + (k_{21} - \beta) e^{-\beta t} \right)
\]

\[
U = k_{10} \cdot D \left( \frac{k_{21}}{\alpha - \beta} \frac{(k_{21} - \alpha)}{\alpha(\alpha - \beta)} e^{\alpha t} - \frac{(k_{21} - \beta)}{\beta(\beta - \alpha)} e^{\beta t} \right)
\]

\[
M = F_e \cdot \left( \frac{\alpha \cdot \beta}{k_{21}} k_u \cdot D \left( \frac{k_{21}}{\alpha - \beta} \right) - \frac{k_{10} \cdot k_u}{\beta(\beta - \alpha)} e^{-\beta t} - \frac{(k_{21} - \beta)}{\beta(\beta - \alpha)} e^{-\beta t} \right)
\]

where \(\alpha\) and \(\beta\) are defined as:

\[
\alpha = \frac{1}{2} \left( (k_{12} + k_{21} + k_{10} + k_m) + \sqrt{(k_{12} + k_{21} + k_{10} + k_m)^2 - 4k_{21}(k_{10} + k_m)} \right)
\]

\[
\beta = \frac{1}{2} \left( (k_{12} + k_{21} + k_{10} + k_m) - \sqrt{(k_{12} + k_{21} + k_{10} + k_m)^2 - 4k_{21}(k_{10} + k_m)} \right)
\]

Pharmacokinetic parameters were obtained by the Gauss-Newton least squares method using the pharmacokinetic data analysis software, WinNonlin standard Ver. 1.5 (Scientific Consulting). The serum concentration of FT \(C\), cumulative excretion amount of FT \(U\), and cumulative excretion amount of Nor–FT \(M\) at each time were inputs. The initial value of each parameter was set to Ishii’s value\(^1\), and the analysis range was set to 0–10 times Ishii’s value. The other parameters, \(k_m, k_{12}, A UC, A UMC, CL, MRT, Vัส\), conclusive excretion amount of FT and Nor–FT, \(U^{\infty}\) and \(M^{\infty}\) were defined as shown below.

\[
k_m = \left( \frac{\alpha \cdot \beta}{k_{21}} \right)
\]

\[
k_{12} = \alpha + \beta - k_{21} - k_{10} - k_m
\]
Evaluation of CYP3A4 Activity

The urinary cortisol (F) and 6β-hydroxycortisol (6β-OH-F) concentrations were determined by Inoue's method\textsuperscript{13} of HPLC determination using fludrocortisone as an internal standard after conversion to fluorescence derivative using 1,2-diamino-4,5-methylenedioxybenzene. The CYP3A4 activity was estimated by the 6β-OHF/F molar concentration ratio in 1 ml of patient urine.

Statistics and Correlation

Significant difference was evaluated by the paired t-test and the level of significance was chosen as $p < 0.05$. The correlation was evaluated by the correlation coefficient, $r$, from the regression line and significant difference was a value of $r$ in excess of 0.7.
FT, the determination limit was 200 ng/ml and the reproducibility was 13.4% (RSD) in the same concentration. It is superior to previous methods using GC or HPLC. For urinary FT, the determination limit was 400 pg/ml and the reproducibility was 16.7% (RSD) in the same concentration. For urinary Nor-FT, the determination limit was 10 ng/ml and the reproducibility was 4.0% (RSD) in the same concentration. The accuracy of these methods is adequate to determine for FT or Nor-FT in urine.

Typical gas chromatograms of isotopic separation for serum FT are shown in Fig. 3. No endogenous compounds or concomitant drugs interfered with the detection of FT or FT-2H19. Serum concentration versus time profiles for FT in 17 patients are shown in Fig. 4. The time of serum collection was limited to 180 minutes for dependence of the operation. There were individual differences in serum levels of FT grater than 10-fold. This variation was not associated with differences of pathology or operation technique.

Urine samples were collected for up to 480 min in the ICU or patients' rooms. Typical gas chromatograms of isotopic separation for urinary FT or Nor-FT are shown in Fig. 5. No endogenous compounds or concomitant drugs interfered with the detection of FT or Nor-FT and its deuterated analogues. In Fig. 6, there were large differences between individuals in the cumulative excretion amounts of FT as a reflection of serum concentration. In the patient with the highest serum FT, the cumulative excretion amount of FT was the largest that over 10% of dose. Similarly, for cumulative excretion of Nor-FT, individual differences were observed as shown in Fig. 7. No relationship between the cumulative excretion amounts of FT and Nor-FT were observed.

Previous studies have reported pharmacokinetics of FT being solved with 2 or 3-compartment models. Reilly et al. reported that a 3-compartment model was inappropriate for FT, because the predicted plasma concentration varied between 2-
3-compartment model results using computer simulation from previous reported pharmacokinetic parameters. Furthermore, the terminal elimination half-life of FT by a 3-compartment model was reported to be 4-8.4 hr. The sample collection time was no more than 3 hr in this study, so we selected a 2-compartment model for FT.

The main metabolite of FT was reported to be Nor-FT in animals and in humans. As shown in Fig. 8, we have reported that FT was metabolized to Nor-FT, p-hydroxy-FT (FT-p-OH), (ω-1)-hydroxy-FT (FT-(ω-1)-OH) and desphenylethyl-(ω-1)-hydroxy-FT (Nor-(ω-1)-OH) in patient urine during 24 hr after continuous infusion FT (2-3 mg/body during 20-30 min). The excretion percentages of the dosage were 8.2-25.2% (Nor-FT), 2.9-5.6% (FT-p-OH), under

![Fig. 7 Cumulative excreted amounts versus time for Nor-FT in urine from patients after administration of FT (5 µg/kg i.v.)](image)

![Fig. 8 Metabolic pathway of FT](image)

![Fig. 9 An example of time course of FT and Nor-FT in patient No. 10](image)
1% (FT-(ω-1)-OH or Nor-(ω-1)-OH) and 0.7-3.6% (FT). Thus, in our constructed model, the metabolic pathway of FT was assumed to be two routes that metabolize to Nor-FT and the others containing FT-p-OH. Nor-FT was excreted to urine without further metabolic exchange.

The pharmacokinetic parameters were solved with the 2-compartment model including the metabolic process using the time profiles of serum FT concentration and excretion amounts of FT and Nor-FT in urine. The predicted curve of time course for FT and Nor-FT was adapted to the FT kinetics as shown in Fig. 9. Akaike's information criterion (AIC) from the parameters of each patient ranged from 40 to 159 (mean=±SD, 82.5±32.2).

The mean values and standard deviations of pharmacokinetic parameters are shown in Table II. The comparative table of pharmacokinetic parameters, together with that of a previous report, is shown in Table III. In this table, k10 is the elimination rate constant of FT to external that corresponds to the sum of k10 and km in our model. The parameters obtained from this study are not significantly different from those of previous reports.

There was a significant correlation between bleed volume and clearance (r=0.73). This correlation assumed transition of FT to external by bleeding, but no correlation was found between pharmacokinetic parameters and other physical parameters such as age, height, weight, body mass index (BMI), and infusion volume. In Table II, the revealing considerable differences were noticed in k10, k31, and km between individuals. The k10 was affected by renal function. It was reported that the clearance of FT was markedly decreased in patients with high blood urine nitrogen (BUN) concentration. But in this study, patients had no renal disease, the reason for k10 variation was not pronounced. The k21 was affected by the distribution of FT from peripheral to central. The back-flow of FT from skeletal muscle to blood by physical movement was reported.

The km was affected by metabolic process. In this study, the excretion rate (% of Dose) of Nor-FT up to 6 hr after administration was 7.1-50.2% (mean 17.2%), which was larger than the FT excretion rate (0.03-3.48%, mean 1.19%). In the case of our previous study by GC-MS analysis, urinary extraction of FT and Nor-FT were 0.7-3.6% and 8.2-25.2% after continuous infusion FT (2-3 mg/body during 20-30 min), and 0.4-3.9% and 27.1-55.4% after bolus injection (0.5 mg/body). In this study too, the predicted final excretion rates of FT and Nor-FT were 0.14-15.77% (mean 4.30%) and 7.36-99.38% (mean 55.12%), respectively. These results indicated that dealkylation was the main route of FT metabolism.

In this way, the pharmacokinetics of FT and Nor-FT are compatible with the 2-compartment model including the metabolic process, and Nor-FT production has an influence on FT elimination. In a previous report, a drug metabolizing enzyme, CYP3A4, metabolized FT to Nor-FT. The CYP3A4 activity is thought to be a dominant factor of FT pharmacokinetics in patients. We compared Nor-FT excretion with CYP3A4 activity estimated from urinary 6β-hydroxycortisol (6β-OHF) and cortisol (F) ratio by Inoue's method. We determined cortisol and 6β-hydroxycortisol in the urine before operation to avoid the affects of anesthesia. Urinary concentrations of F, 6β-OHF, their ratio, and CYP3A4 activity in patients are shown in Table IV. Inaccurate activities

### Table II Pharmacokinetic parameters of FT in patients

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<td>Vdss(l/kg)</td>
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### Table III Pharmacokinetic parameters of FT in previous reports

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<td>k10(min⁻¹)</td>
<td>0.00210</td>
<td>0.100</td>
<td>0.0115</td>
<td>0.0282</td>
<td>0.0792*</td>
</tr>
<tr>
<td>k12(min⁻¹)</td>
<td>0.0980</td>
<td>0.366</td>
<td>0.0505</td>
<td>0.103</td>
<td>0.221</td>
</tr>
<tr>
<td>km(min⁻¹)</td>
<td>0.0450</td>
<td>0.0300</td>
<td>0.0177</td>
<td>0.0224</td>
<td>0.0496</td>
</tr>
</tbody>
</table>

* k10+km
were obtained in some samples (No. 1, 5, 8 and 9) by interfering peaks on their chromatograms. The activities were not correlated with excretion rate (% of Dose) of FT or Nor-FT, excretion rate ratio (Nor FT/FT), or pharmacokinetic parameter km of FT or Nor-FT. FT was reported34) to have a high hepatic extraction ratio (0.8). These results suggest that FT elimination was dominated by hepatic blood flow in preference to CYP3A4 activity. Palkama et al. reported35) that there were no significant difference in pharmacokinetics of FT using concomitant administration FT (3,ug/kg) with CYP3A4 inhibitor, itraconazole. For the same reason, CYP3A4 activity would not reflect FT elimination in our study which used a low dose of FT (5µg/kg).

In summary, the pharmacokinetics of FT and Nor-FT are compatible with a 2-compartment model including the metabolic processes, and the calculated parameters showed differences between individuals. The CYP3A4 activity from urine steroid was not reflected in FT elimination at low doses.

In a previous report, a reduction of hepatic blood flow was suggested in high-dose FT36). Further studies are needed to examine the individual variations in the elimination process of FT for high-dose anesthesia.

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References
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