Pharmacokinetics/Pharmacodynamics of Acetaminophen Analgesia in Japanese Patients with Chronic Pain

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Acetaminophen (APAP) is a popular analgesic. In the present study, we characterized the pharmacokinetics and pharmacodynamics of APAP in the Japanese. Five healthy volunteers were administered 1000 mg of APAP orally. Five patients with chronic pain were administered the optimal oral dose of APAP ranging from 600 to 1000 mg to allow for an adequate analgesic effect. Plasma APAP and APAP metabolite concentrations were measured in the volunteers, plasma APAP concentrations and pain scores using a visual analog scale were measured in the patients with chronic pain. Patient data were fitted to a first-order absorption one-compartment model with delayed effects accounted for by an effect compartment. A sigmoid E_{max} model was used as the pharmacodynamic model. Acetaminophen-cysteine metabolites, which are conjugates of the toxic metabolite *N*-acetyl-*p*-benzoquinone-imine, were detected in the plasma at levels lower than 0.2 μg/ml, but no side effects were observed. The pharmacokinetic and pharmacodynamic parameter (mean±S.D.) estimates were as follows: clearance, 18.7±4.7 l/h; distribution volume, 30.9±6.8 l; absorption rate constant, 2.4±1.3 h^{-1}; rate constant for the elimination of APAP from the effect compartment, 1.3±0.5 h^{-1}; maximum pain relief score, 4.6±2.2 units; effect compartment concentration at 50% maximum, 2.0±1.2 μg/ml; and sigmoid factor, 1.3±0.7. These results suggest that these parameters can be used to determine an effective APAP dosage regimen for Japanese patients with chronic pain.

Key words acetaminophen; pharmacokinetic–pharmacodynamic modeling; chronic pain

Acetaminophen (APAP) is a popular analgesic worldwide, but in Japan, APAP is used mainly as an antipyretic in children. APAP is rarely used as an analgesic in Japan, because the recommended dosage of APAP in Japan (less than 1500 mg/d)[1] is lower than that in United States (less than 4000 mg/d).[2]

APAP is metabolized by UDP-glucuronosyltransferase, sulfotransferase and cytochrome P450 (Fig. 1). There is substantial interindividual variability in APAP glucuronidation,[3] and polymorphisms of UDP-glucuronosyltransferase have been reported.[4,5] APAP is metabolized by cytochrome P450 2E1 to the toxic metabolite *N*-acetyl-*p*-benzoquinone-imine (NAPQI). The genotype frequency of cytochrome P450 2E1 differs with ethnicity.[6] The degree of chlorzoxazone clearance, which is used as a phenotypic probe of CYP2E1 enzyme activity in Japanese, is lower in Caucasians.[7] Therefore, the pharmacokinetics of APAP in high doses in Japanese patients needs to be clarified to determine whether the use of APAP as an analgesic is safe.

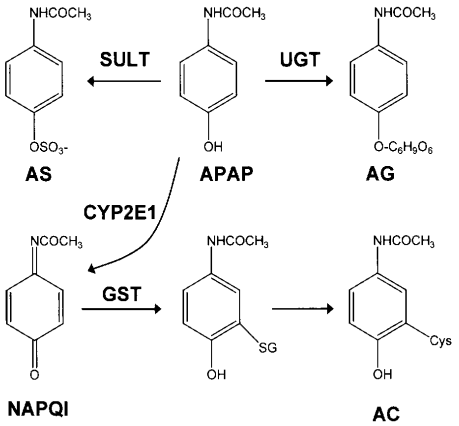

Fig. 1. Metabolism of Acetaminophen

Acetaminophen is metabolized by cytochrome P450 2E1 to the toxic metabolite *N*-acetyl-*p*-benzoquinone-imine, which is conjugated by glutathione to cysteine metabolites. APAP; acetaminophen, AS; acetaminophen sulfate, AG; acetaminophen glucuronide, NAPQI; *N*-acetyl-*p*-benzoquinone-imine, AC; acetaminophen cysteine metabolites, SULT; sulfotransferase, UGT; UDP-glucuronosyltransferase, GST; glutathione S-transferase, CYP2E1; cytochrome P450 2E1.

The relationship between pain relief and APAP concentration has been investigated in German[8] and Danish[9] postoperative patients. In children undergoing adenotonsillectomy, the pharmacokinetic-pharmacodynamic model has been described.[10] However, pain sensitivity differs among ethnic groups.[11] A better understanding of the dose–effect relationship in Japanese is needed to control chronic pain. There are no data describing the pharmacokinetics and pharmacodynamics of APAP and its metabolites in the Japanese. An understanding of the relationship between the analgesic effect and the time after APAP administration is important for determining the dosage of APAP for the treatment of chronic pain. The aims of this study are to characterize the pharmacokinetics and pharmacodynamics of APAP and to determine an effective APAP regimen in Japanese patients with chronic pain.

MATERIALS AND METHODS

Materials APAP, acetaminophen glucuronide (AG), theophylline, ammonium acetate, and perchloric acid were obtained from Sigma Chemical (St. Louis, MO, U.S.A.). Acetaminophen sulfate (AS) and acetaminophen-cysteine (AC)

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Table 1. Patients' Characteristics

Patient ID	1	2	3	4	5	Mean	S.D.
Male/female	F	F	F	F	M		
Age (years)	74	54	58	40	49	55	13
Weight (kg)	55	52	74	51	70	60	11
AST (IU/l)	24	16	35	16	19	22	8
ALT (IU/l)	14	11	52	4	23	21	19
Scr (mg/dl)	1	0.6	0.5	0.6	1	0.7	0.2

AST; aspartate aminotransferase. ALT; alanine aminotransferase. Scr; serum creatinine.

were donated by Showa Yakuhin Kako (Tokyo, Japan). All chemicals and reagents were of analytical or chromatographic grade.

Study Design Five healthy volunteers and five patients with chronic pain who were not using any other analgesics were included in this study after giving informed consent. The study protocol was approved by the ethics review committee of Toho University Ohashi Medical Center. The patients' characteristics are shown in Table 1. None of the patients presented with major renal or hepatic impairment.

The five healthy volunteers received 1000 mg of APAP orally. The volunteers fasted from after their last meal on the day preceding APAP administration to 3 h after APAP administration. A cannula was inserted into an antecubital vein to facilitate the sampling of venous blood. Blood was obtained before APAP administration and 15, 30, and 45 min, and 1, 2, 3, 4, and 6 h after the administration. After centrifugation (3000 rpm, 10 min), plasma samples were stored at −30 °C until assayed.

The study of the five patients with chronic pain was divided into two phases. In the first phase, we determined the optimal dose that allows for an adequate analgesic effect of APAP (Calonal®, Showa Yakuhin Kako). Each patient received an escalating oral dose until an apparent effect of APAP analgesia was observed. The upper limit of the APAP dose was 1000 mg as a single dose and 3000 mg as a daily dose. In the second phase, each patient was administered APAP tablets at the optimal dose determined in the first phase with 200 ml water. The patients fasted from after their last meal on the day preceding APAP administration to 3 h after APAP administration. A cannula was inserted into an antecubital vein to facilitate the sampling of venous blood. Blood was obtained before APAP administration and 15, 30, and 45 min, and 1, 2, 3, 4, and 6 h after the administration. Chronic pain was assessed using a visual analog scale (VAS; 0=no pain, 10=worst pain imaginable). Pain scores were recorded at every blood sampling. Pain relief scores were obtained by subtracting the pain score from the initial pain score. After centrifugation (3000 rpm, 10 min), plasma samples were stored at –30 °C until assayed.

Acetaminophen Assay To study the healthy volunteers, APAP, AG, AS, and AC concentrations were determined using the modified high performance liquid chromatography (HPLC) method described by Brunner and Bai.[12] The plasma samples were deproteinated by adding of 6% (v/v) perchloric acid in water containing theophylline as an internal standard. The samples were mixed using a vortex for 5 s and then centrifuged (14000 rpm, 10 min, centrifuge 5417R, Eppendorf). The supernatant was injected into the HPLC system. HPLC was performed using a CAPCELL PAK C18 column (4.6 mm×150 mm, Shiseido) by isocratic elution with a mobile phase of 10 mM ammonium acetate (pH 6.0)–acetonitrile (95 : 5, v/v) and ultraviolet detection (SPD-10A, Shimadzu) at 254 nm. The flow rate was 0.8 ml/min. The concentrations of the metabolites were calculated as APAP equivalents. In the study of the patients with chronic pain, APAP concentration was determined by fluorescence polarization immunoassay at Mitsubishi Kagaku Bio-Clinical Laboratories (Tokyo, Japan).

Data Analysis To study both the volunteers and the patients, noncompartmental analysis[13] using the WinNonlin pharmacokinetic software package (Pharsight Corporation, Mountain View, CA, U.S.A.) was performed to determine the pharmacokinetic parameters. The area under the concentration–time curves (AUC) was extrapolated to infinity for APAP and its metabolites. The peak APAP concentration (C_{max}) and the time to reach C_{max} (T_{max}) were obtained directly from the raw data. To study the patients with chronic pain, a first-order absorption one-compartment model with delayed effects accounted for by an effect compartment was used.[14] The model was parameterized in terms of the absorption rate constant (k_a), apparent volume of distribution (V_d), total clearance (CL) after oral administration, and the rate constant for the elimination of APAP from the effect compartment (k_{eo}). APAP was administered orally, and CL and V_d were confounded by bioavailability. The pharmacodynamic model was used as a sigmoid E_{max} model according to the equation:

$$E=(E_{max}\times Ce^{\gamma})/(EC_{50}{}^{\gamma}+Ce^{\gamma}),$$

where E, E_{max}, Ce, EC_{50} and γ represent the pain relief score, the maximum pain relief score, the APAP concentration in a hypothetical effect compartment, the APAP Ce that corresponds to 50% of the E_{max}, and the sigmoid factor, respectively. The fitting process was a simultaneous estimation by a nonlinear least squares fit of the model to the APAP concentration and the pain relief score profiles using the WinNonlin pharmacokinetic software package (Pharsight Corporation, Mountain View, CA, U.S.A.).

Simulation Using Pharmacokinetic/Pharmacodynamic Parameter Estimates Using mean pharmacokinetic and pharmacodynamic parameters, simulations were performed to predict the time course of APAP effects for oral doses ranging from 250 to 4000 mg with a varied dosage regimen. For each simulation, a summary parameter, namely, the effective time during which the pain relief score was higher than three VAS units, was used to characterize the time course of each endpoint after APAP administration.

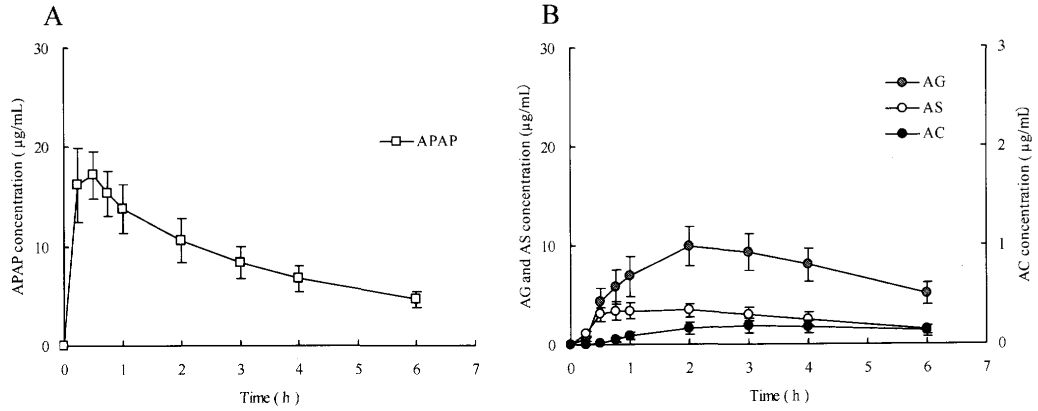

Fig. 2. APAP (A) and Metabolites (B) Concentrations in Five Healthy Volunteers

The concentrations of the metabolites were calculated as APAP equivalents. Plots represent mean±S.D.

Table 2. Noncompartmental Analysis for APAP in Healthy Volunteers

Volunteer ID		1	2	3	4	5	Mean	S.D.
APAP	*AUC* (μg·h/ml)	96.5	68.0	87.8	72.2	64.7	77.8	13.7
	V_d/F(l)	66.4	52.6	79.4	52.9	97.4	69.7	19.0
	CL/F (l/h)	11.4	13.9	15.4	10.4	14.7	13.2	2.2
	C_{max} (μg/ml)	21.5	20.0	14.4	18.2	14.2	17.7	3.3
	T_{max} (h)	0.25	0.5	0.5	0.5	0.5	0.5	0.1
AC	*AUC* (μg·h/ml)	4.0	1.0	6.0	3.8	3.6	3.7	1.8
AG	*AUC* (μg·h/ml)	53	69	64	53	90	66	15
AS	*AUC* (μg·h/ml)	23.0	11.6	22.6	19.0	28.8	21.0	6.3

Dose: 1000 mg.

RESULTS

The concentrations of APAP and its metabolites in healthy volunteers are shown in Fig. 2. Table 2 shows the *AUC* values of APAP and its metabolites. The *AUC* for AC was small compared with those for other metabolites. No side effects were observed in the healthy volunteers.

In the patients with chronic pain, the optimal mean (range) APAP dose that allowed for an adequate analgesic effect of APAP was 800 (600—1000) mg as a single dose. The APAP concentrations, pain scores, and pain relief score profiles are shown in Fig. 3. The APAP concentrations reached the maximum concentration 30 min after drug administration in four patients. In those four patients, the pain score decreased maximally 45 min after drug administration. The effects of APAP were delayed compared with the APAP concentrations. In the other patient, the APAP concentration increased until 2 h after administration. The pain score decreased maximally 30 min after administration. No side effects were observed in the patients.

Plotting pain relief score against APAP concentration revealed a counterclockwise hysteresis relationship (Fig. 4). The individual pharmacokinetic and pharmacodynamic parameters are shown in Table 3. Figure 5 shows the simulated relationship between the daily dose of APAP and the effective time during which the pain relief scores were higher than three VAS units in five dosage schedules.

DISCUSSION

There is few information concerning the analgesic effect–time relationship of APAP in the Japanese. The characteriza-

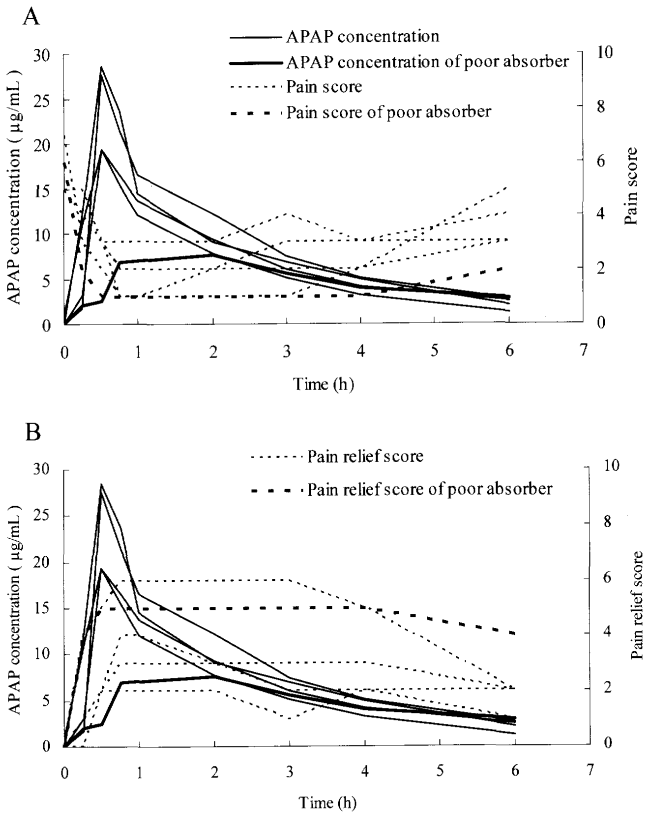

Fig. 3. APAP Concentration and Pain Score Profiles (A), and APAP Concentration and Pain Relief Score Profiles (B) in Five Patients with Chronic Pain

Pain relief scores were obtained by subtracting the pain score from the initial pain score. The bold line and the bold dashed line represent the data of a patient with a delay in the time to reach the peak APAP concentration. The thin lines and thin dashed lines represent the other patients.

Table 3. Pharmacokinetic/Pharmacodynamic Parameters for APAP in Chronic Pain Patients

Patient ID	1	2	3	4	5	Mean	S.D.
V_d/F (l)	24.7	27.0	28.8	31.7	42.1	30.9	6.8
CL/F (l/h)	16.1	12.8	18.2	21.9	24.6	18.7	4.7
k_a (1/h)	3.48	3.85	1.89	2.06	0.61	2.4	1.3
k_{eo} (1/h)	1.35	0.92	0.53	1.52	1.94	1.3	0.5
E_{max}	6.48	3.84	1.99	3.44	7.38	4.6	2.2
EC_{50} (μg/ml)	2.34	2.92	1.56	3.12	0.14	2.0	1.2
γ	1.41	1.85	1.97	1.24	0.19	1.3	0.71
Dose (mg)	800	600	1000	800	800	800	141

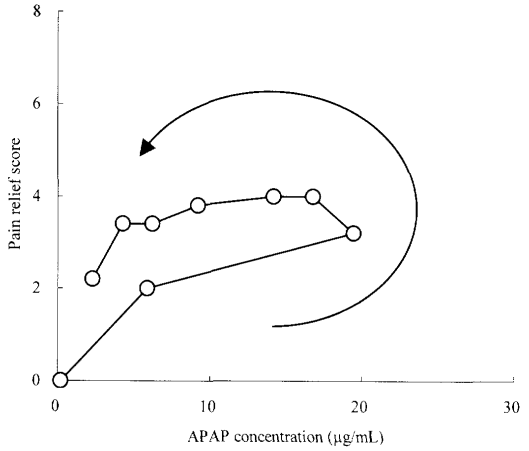

Fig. 4. Relationship between APAP Concentration and Pain Relief Score in Five Patients with Chronic Pain

Plots represent mean values.

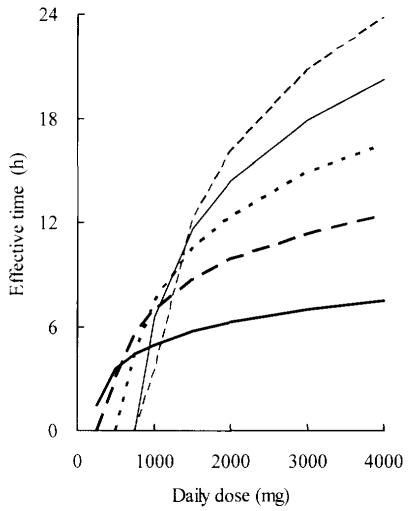

Fig. 5. Relationship between the Daily Dose of APAP and the Effective Time of Five Dosage Schedules

Effective time was defined as the time during which the pain relief scores were higher than three VAS units. The dosage schedules were from once to five times a day. ——, once a day; — — —, twice a day; - - - - -, 3 times a day; ———, 4 times a day; --------, 5 times a day.

tion of the effect–time relationship is useful for determining a dosage schedule for APAP. The main objective of our pharmacokinetic and pharmacodynamic study is to characterize the pharmacokinetics of APAP and its metabolites for a single 1000 mg dose of APAP and the analgesic effect-time course of APAP after a single high dose in Japanese patients with chronic pain.

Hepatotoxicity is a consequence of APAP overdose due to the increased metabolism of APAP through oxidation, resulting in an increase in NAPQI concentration. In case of an overdose, unconjugated NAPQI binds to intracellular hepatic macromolecules to induce cell necrosis and damage.[15] Because NAPQI is conjugated by glutathione into cysteine metabolites, the amount of such conjugates was considered to be a measure of the endpoint of hepatotoxicity in the study. The *AUC* of AC was only 5% of that of APAP after a 1000 mg dose of APAP (Table 2). This value is almost equal to that reported by Chan *et al.*[16] (5%) in Chinese diabetic patients after 20 mg/kg body weight APAP administration. Prescott *et al.* reported that plasma AC was not detectable after a single 1000 mg dose of APAP in the healthy volunteers in Scotland,[17] because it was considered that APAP was scarcely metabolized to NAPQI after a 1000 mg dose of APAP. The *AUC* values for AG and AS were almost equal to those reported by Prescott *et al.*[17] The APAP glucuronidation and sulfate conjugation activity in the Japanese were similar to those in Caucasians. The APAP concentration 4 h after administration in this study was 6.7 μg/ml, while toxic concentrations higher than 120—300 μg/ml appeared 4 h after administration.[18,19] Side effects were not observed in this study. Therefore, a single 1000 mg dose of APAP was considered to be a safe analgesic dose for the Japanese.

There were no significant differences in V_d/F and CL/F calculated by noncompartmental analysis between the patients with chronic pain and the healthy volunteers ($p=0.12$, 0.11, respectively by unpaired t-test, data not shown). The pharmacokinetics of APAP have been reported in patients with chronic renal failure,[17] portal hypertension,[20] and chronic liver disease.[21,22] In patients with these diseases, the APAP half-life was long compared with that in healthy volunteers. Patients with chronic pain tend to take analgesics over a long period. Although it is necessary to note the effect of these diseases on APAP pharmacokinetics, in this study there was no significant difference in the pharmacokinetics of APAP between the healthy volunteers and the patients with chronic pain. We determined that a single 1000 mg dose of APAP can be safely used for Japanese patients with chronic pain.

Because the onset of the analgesic effect of APAP was delayed compared with the APAP concentration and the counterclockwise hysteresis relationship was observed, we used a first-order absorption one-compartment model with delayed effects accounted for by an effect compartment.[23] The hysteresis relationship represents an apparent temporal displacement between APAP concentration and pain relief. The APAP concentration and pain relief profiles in Japanese patients with chronic pain can be described using a one-compartment with an effect compartment model. The pharmaco-

kinetic and pharmacodynamic parameters of APAP were obtained from data from Japanese patients with chronic pain. A delayed onset of the effects have been observed in children.[10,24] In those studies, the delayed onset of the effects is described by a one-compartment with an effect compartment model. The equilibration half-times as an index of the delayed onset of the effect are 1.3,[10] 0.88[24] h. The equilibration half-time in this study was 0.53 h. Pickering *et al.* reported that the analgesic effect of APAP involves a central serotonergic mechanism, including an indirect interaction of APAP with serotonergic receptors.[25] The delayed onset of the effect and the counterclockwise hysteresis relationship might be due to this pharmacologic mechanism.

Pain control for patients with chronic pain requires continuous pain relief. We simulated the effective time during which the pain relief scores were higher than three VAS units using pharmacokinetic and pharmacodynamic parameter estimates (Fig. 5). The time during which the pain relief scores were higher than three VAS units was considered to represent the period of pain relief. The recommended dosage in United States is less than 4000 mg a day.[2] In Japan, the dosage is allowed to be increased up to 3000 mg a day at a physician's discretion. Because the APAP glucuronidation and sulfate conjugation in this study were equal to those in Caucasians,[17] the simulations were performed for dosages ranging from 250 to 4000 mg a day and each dosage was administered as either a single dose or divided into 2 to 5 doses. The simulation suggests that the dosage plan (500 mg× 3 times/d), as suggested by the package insert,[1] relieves pain for only 10.2 h. Relief from the pain for 16 h requires that the daily dose be increased to 2000 mg divided into five doses or 2400 mg divided into four doses for Japanese patients with chronic pain. These results suggest that the dosage of APAP needs to be higher than that recommended by the package insert for Japanese patients with chronic pain. Generally, Japanese and Caucasians standard body weights are 60 and 70 kg, respectively. Considering that the Japanese build is smaller than that of Caucasians, the dosage of APAP for Japanese patients with chronic pain may need to be lower than that in United States. An aminotransferase elevations associated with daily intake of 4000 mg of APAP in healthy adults has been reported.[26] An APAP toxicity in the case of multiple doses and higher dosages in the Japanese need to be investigate using AC and a new biomarker,[27] ophthalmic acid, which indicates hepatic glutathione consumption as an APAP overdose.

In conclusion, we characterized the APAP concentration and pain relief score profiles in Japanese patients with chronic pain after a single high dose of APAP. An understanding of the pharmacokinetic and pharmacodynamic parameters for APAP will allow for an effective dosage plan.

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