Pharmacokinetics and Variation in the Clearance of Oxycodone and Hydrocotarnine in Patients with Cancer Pain

Hideya KOKUBUN,^{*,a} Misako FUKAWA,^a Motohiro MATOBA,^b Sumio HOKA,^c Yasuhiko YAMADA,^d and Kazuo YAGO^a

^aDepartment of Pharmacy, Kitasato University Hospital; ^cDepartment of Anesthesiology, Kitasato University School of Medicine; 1–15–1 Kitasato, Sagami-hara, Kanagawa 228–8555, Japan; ^bNational Cancer Center, Center for Cancer Control and Information Services, Cancer Information Services and Surveillance Division, Cancer Information Services Section; 5–1–1 Tsukiji, Chuo-ku, Tokyo 104–0045, Japan; and ^dDepartment of Clinical Evaluation of Drug Efficacy, School of Pharmacy, Tokyo University of Pharmacy and Life Science; 1432–1 Horinouchi, Hachioji, Tokyo 192–0392, Japan. Received March 27, 2007; accepted August 17, 2007; published online August 21, 2007

Compound injections of oxycodone and hydrocotarnine are currently used as one of the treatment options for some cases with cancer pain. However, there have been no reports examining the factors that influence oxycodone and hydrocotarnine clearance, so detailed examination is necessary. As for hydrocotarnine, there have been no reports examining the pharmacokinetics. Therefore in this study, we determined the pharmacokinetics of oxycodone and hydrocotarnine in patients with cancer pain. The study was conducted on 19 patients, in whom pain control was attempted by using the compound injections of oxycodone and hydrocotarnine. We used HPLC-electrochemical detector (ECD) to determine oxycodone and hydrocotarnine serum concentrations, and used the nonlinear least-squares method (MULTI) for calculation of the pharmacokinetic parameters. Furthermore, we examined the factors that influence the clearance of oxycodone and hydrocotarnine by multiple regression analysis (step wise method). The pharmacokinetic parameters were as follows: Oxycodone; $V_d=226.7\pm105.5$ l (mean $\pm$ S.D.), $CL=37.9\pm25.1$ l/h, $t_{1/2}=4.1\pm1.9$ h. Hydrocotarnine; $V_d=276.8\pm237.2$ l, $CL=95.1\pm64.3$ l/h, $t_{1/2}=2.0\pm0.7$ h. The clearance of oxycodone represented by a regression formula was significantly correlated to the age, the presence or absence of within 7 d on the death or liver metastasis, or of the heart failure of the patients. The clearance of hydrocotarnine represented by a regression formula was significantly correlated to the presence or absence of within 7 d on the death or liver metastasis, or of the heart failure of the patients. The clearance also indicated that oxycodone concentration in the blood was likely to be higher in patients having these factors. Oxycodone/hydrocotarnine compound injections should be used with caution and dose reduction may be necessary in such populations.

Key words pharmacokinetics; oxycodone; hydrocotarnine; pavinal[®] injection; cancer pain; opioid

Palliative care for cancer pain following the WHO's three step ladder is now world wide established therapy. Recently in Japan, new strong opioids have been placed on the market in succession—transdermal fentanyl (Durotep[®] Patch) in March 2002, and oral controlled-release oxycodone tablets (Oxycontin[®]) in July 2003. However, supplies of drug formulations for potent opioids are still insufficient. There is no oxycodone preparation available in a single injection dosage form. Nowadays, along with the increase in the use frequency of controlled-release oxycodone, injectable oxycodone has become the opioid of choice. For those cases, we select the compound injections of oxycodone and hydrocotarnine that has been used so far. However, it is impossible to design a detailed dosage that matches the various patients' conditions because no report has examined the variation factors of oxycodone and hydrocotarnine clearances. As for hydrocotarnine, there are no reports that examine the pharmacokinetics. Therefore, in this study, we measured the serum concentration levels of oxycodone and hydrocotarnine in patients with cancer pain in order to determine the pharmacokinetics of these drugs. Furthermore, the pharmacokinetic parameters of each drug were computed and the variation factors of drug clearance were evaluated.

MATERIALS AND METHODS

Patients The study was conducted on 19 patients with

cancer pain who had been admitted to the Department of Anesthesiology of our hospital between February 2003 and October 2006, and in whom pain control was attempted by using the compound injections of oxycodone and hydrocotarnine (pavinal[®] injection). Approval for the use of the compound injections of oxycodone and hydrocotarnine and determination of the serum concentration were obtained from the ethics committee of our hospital prior to the start of the study. In addition, written informed consent was obtained from each patient or his/her family prior to his/her participation in the study.

Dosing and Sampling Procedures. Dosing and Sampling The compound injections of oxycodone and hydrocotarnine were administered continuously intravenously or subcutaneously, or as an intravenous infusion. Blood samples were collected at the following schedules for the determination of oxycodone or hydrocotarnine serum concentrations—continuous intravenous or subcutaneous infusions: 4, 8, 12, 24 and 48 h after the infusion; intravenous drip: just after the infusion, 2 and 6 h after the infusion.

Serum Concentration Measuring Oxycodone and hydrocotarnine serum concentrations were determined by HPLC (high-performance liquid chromatography) using ECD (electrochemical detector), using the method we had developed.¹⁾ Chromatograms were obtained using a PU-2080 pump (Nihon Bunko) equipped with an electrochemical detector, Coulochem II5200A and MODEL 5020 (MCMEDICAL).

* To whom correspondence should be addressed. e-mail: kokubun@kitasato-u.ac.jp

An XTerra® RP18 column (5 μ m, 4.6 mm $\times$ 50 mm i.d., Waters, Japan) at an ambient temperature (40 °C) was used to separate the oxycodone, hydrocotarnine, and codeine (internal standard). The separation of the oxycodone, hydrocotarnine and codeine was achieved using an eluent of methanol : acetonitrile : 5 mM pH 8 phosphate buffer (2 : 1 : 7). The voltage of the working electrode of the electrochemical detector was set at 800 mV. Blood samples (2.0 ml) were immediately centrifuged at 3000 rpm for 10 min. To 1.0-ml serum sample (standard or unknown) was added 100 μ l codeine (internal standard, 25 ng/ml), 0.5 ml 4 M NaOH, and 4 ml butyl chloride. The samples were then mixed for 15 min, centrifuged for 10 min at 3000 rpm, and the butyl chloride (top layer) was transferred to a clean glass tube. The remaining aqueous layer was extracted by another 4 ml butyl chloride using the same procedure. The combined butyl chloride extract was then evaporated. The dried residue was reconstituted in 200 μ l mobile phase, and 40 μ l solution was injected into the HPLC.

Data Analysis The pharmacokinetic parameters were calculated by the nonlinear least-squares method (MULTI)^{2,3)} that used the one-compartment model. And multiple regression analysis (step wise method) was used to examine the influence on the clearance of oxycodone and hydrocotarnine. We established the following indicators as predictive factors—age, gender, weight, average blood pressure, AST, ALT, serum creatinine, creatinine clearance, within 7 d on the death, liver metastasis or heart failure.

All statistical analyses were performed with SPSS 14.0J (SPSS Japan Inc.) for Windows statistical package. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Patients Background

The backgrounds of subjects were

as follows: 14 males and 5 females; blood collection time-points, 42; age, ranging from 36 to 79 years; body weight, ranging from 40.3 to 71.8 kg. These data indicate that this patients population was derived from a wide range of backgrounds and represented a general population of patients suffering from cancer pain. The general characteristics of the subjects are listed in Table 1.

Serum Concentration and Pharmacokinetic Parameters

Total sampling points were 42, and in 8 patients it was

Table 2. Pharmacokinetic Parameter of Oxycodone and Hydrocotarnine in 19 Patients with Cancer Pain

Case	Oxycodone			Hydrocotarnine		
	V_d (l)	CL (l/h)	$t_{1/2}$ (h)	V_d (l)	CL (l/h)	$t_{1/2}$ (h)
1	448.2	40.0	7.8	251.2	70.3	2.5
2	287.7	114.6	1.7	747.4	199.7	2.6
3	90.7	13.0	4.8	94.3	24.8	2.6
4	184.5	39.2	3.3	*	*	*
5	220.0	63.0	2.4	*	*	*
6	224.3	35.1	4.4	233.9	75.5	2.1
7	—	65.7	—	—	218.3	—
8	—	35.4	—	—	79.6	—
9	—	42.3	—	—	133.9	—
10	—	15.9	—	—	32.9	—
11	—	12.2	—	—	119.0	—
12	—	19.1	—	—	189.4	—
13	—	23.0	—	—	17.4	—
14	—	18.1	—	—	58.4	—
15	—	19.7	—	—	2.5	—
16	—	57.7	—	—	86.8	—
17	—	17.9	—	—	88.3	—
18	192.4	40.1	3.3	169.4	144.7	0.8
19	166.1	23.7	4.9	164.4	75.2	1.5
Mean	226.7	37.9	4.1	276.8	95.1	2.0
S.D.	105.5	25.1	1.9	237.2	64.3	0.7

* Below detectable limit. Case 7—17: only 1 point of steady state was measured.

Table 1. Patient Demographic Data

Paient No.	Primary disease	Age	Gender	BW ^{a)} (kg)	Dose (mg/d) (as oxycodon)	Administration route	Scr ^{b)} (mg/dl)	Measured CLcr ^{c)} (ml/min)	AST (U/l)	ALT (U/l)	Mean BP ^{d)} of early morning (mmHg)	Days to death (d)	HF ^{e)}	LM ^{f)}
1	Gastric cancer	64	M	52.7	40	Continuous IV ^{g)} infusion	0.74	82.4	84	32	100	31	—	—
2	Olfactory neuroepithelioma	36	M	71.3	40	Continuous SC ^{h)} infusion	0.36	170.5	32	42	105	59	—	—
3	Submandibular cancer	64	M	60.4	184	Continuous IV infusion	0.24	86.5	35	19	94	7	—	—
4	Prostate cancer	78	M	62	16	Continuous SC infusion	0.73	47.5	42	17	90	88	—	—
5	Renal cancer	69	M	58.4	120	Continuous IV infusion	0.75	82.5	37	16	101.5	over 1 year	—	—
6	Malignant melanoma	56	F	44	8	Continuous SC infusion	0.49	95.1	22	23	106	240	—	—
7	Tongue cancer	54	M	62.4	88	Continuous SC infusion	0.55	86.2	15	15	100	249	—	—
8	Breast cancer	52	F	44.6	120	Continuous IV infusion	0.48	76.3	46	39	83	5	—	—
9	Prostate cancer	59	M	71.8	72	Continuous SC infusion	0.58	114.6	67	57	96	72	—	—
10	Multiple myeloma	62	M	66.9	24	Continuous IV infusion	0.35	65.8	376	541	108	4	+	—
11	Multiple myeloma	67	F	50.6	8	Continuous IV infusion	0.5	73.4	81	41	115	115	—	—
12	Breast cancer	76	F	44.8	40	Continuous IV infusion	0.41	64.3	63	78	97	153	—	—
13	Larynx cancer	71	M	49.3	8	Continuous IV infusion	0.6	66.9	62	53	80	47	—	—
14	Renal cancer	61	M	50.8	60	Continuous IV infusion	0.56	110.3	22	48	68.5	35	—	—
15	Prostate cancer	79	M	52.3	8	Continuous IV infusion	0.57	40	16	29	83	109	+	—
16	Breast cancer	51	F	52.7	40	Continuous SC infusion	0.65	90.9	33	29	126	184	—	—
17	Sigmoid colon cancer	74	M	66.6	8	Continuous SC infusion	2.51	20.5	136	71	93	70	—	+
18	Tongue cancer	65	M	40.3	4	IV drip (60 min)	0.37	77.4	12	11	71	60	—	—
19	Rectum cancer	58	M	43.6	132	IV drip (80 min)	0.48	111.3	32	71	86	155	—	+

a) BW, body weight. b) Scr, serum creatinine. c) CLcr, creatinine clearance. d) BP, blood pressure. e) HF, heart failure. f) LM, liver metastasis. g) IV, intravenous. h) SC, subcutaneous.

Fig. 1. Serum Concentration–Time Curve of Oxycodone and Hydrocotarnine after Continuous Intravenous or Subcutaneous Infusion at Each Case (Case 1–6)

Symbol: ●, oxycodone serum concentration; ○, hydrocotarnine serum concentration.

Fig. 2. Serum Concentration–Time Curve of Oxycodone and Hydrocotarnine after Intravenous Drip at Case 18 and 19

Symbol: ●, oxycodone serum concentration; ○, hydrocotarnine serum concentration.

possible to draw blood more than twice. The serum concentration–time curves of oxycodone and hydrocotarnine for all subjects administered as a continuous intravenous infusion or intravenous drip are shown in Figs. 1 and 2. The pharmacokinetic parameters were as follows: Oxycodone; Volume of distribution (V_d) = 226.7 ± 105.51 (mean $\pm$ S.D.), Clearance (CL) = 37.9 ± 25.1 l/h, Elimination half-life ($t_{1/2}$) = 4.1 ± 1.9 h. Hydrocotarnine; V_d = 276.8 ± 237.21 , CL = 95.1 ± 64.3 l/h, $t_{1/2}$ = 2.0 ± 0.7 h (Table 2).

The Factors Influencing the Clearance of Oxycodone and Hydrocotarnine The clearance of oxycodone repre-

sented by a regression formula was significantly correlated to the age, the presence or absence of within 7 d on the death or liver metastasis, or of the heart failure of the patients. Regression expression: oxycodone clearance = $-1.459 \times (\text{age}) - 18.876 \times (\text{within 7 d on the death, liver metastasis or heart failure}) + 134.994$ (multiple correlation coefficient (R) = 0.719, coefficient of determination (R^2) = 0.517, $p = 0.001$) (Table 3). And there was good correlation between hydrocotarnine clearance and the following factors: within 7 d on the death, liver metastasis or heart failure. Regression expression: hydrocotarnine clearance = $73.402 \times (\text{within 7 d on the$

Table 3. Stepwise Multiple Regression

Dependent variable	Clearance of oxycodone	
Independent variable	<i>t</i>	<i>p</i>
Age	-3.768	0.002
Gender	1.713	0.107
Body weight	1.934	0.072
Mean blood pressure	0.269	0.792
AST	-0.651	0.525
ALT	-0.135	0.463
Scr	0.928	0.368
CLcr	-0.032	0.975
Within 7 d on the death, liver metastasis or the heart failure	-2.174	0.045

$n=19$. $y = -1.459(\text{age}) - 18.876$ (within 7 d on the death, liver metastasis or the heart failure) + 134.994. $R^2 = 0.517$.

Dependent variable	Clearance of hydrocotarnine	
Independent variable	<i>t</i>	<i>p</i>
Age	-1.763	0.100
Gender	-0.389	0.703
Body weight	0.610	0.552
Mean blood pressure	0.588	0.566
AST	-0.498	0.626
ALT	-0.181	0.859
Scr	-0.990	0.339
CLcr	1.510	0.153
Within 7 d on the death, liver metastasis or the heart failure	-2.460	0.027

$n=17$. $y = -73.402^*$ (within 7 d on the death, liver metastasis or the heart failure) + 116.395. $R^2 = 0.287$.

Fig. 3. Influence Factors of Oxycodone and Hydrocotarnine Clearance

The oxycodone clearance of group A and B were respectively 43.9 ± 27.2 (mean $\pm$ S.D.) and 20.4 ± 8.8 . While hydrocotarnine clearance were respectively 119.4 ± 64.4 and 50.6 ± 35.1 . The mean clearance of oxycodone and hydrocotarnine were about twice in group A compared with B, and were statistically significant (oxycodone: $p=0.035$, hydrocotarnine: $p=0.044$). Group A: patients whose rest of time to death were 8 d or more, no liver metastasis or no heart failure. Group B: patients who were within 7 d on the death, liver metastasis or heart failure.

death, liver metastasis or heart failure) + 116.395 (multiple correlation coefficient (R) = 0.536, coefficient of determination (R^2) = 0.287, $p=0.027$) (Table 3). Furthermore we divided subjects into 2 groups (group A, B), and compared their oxycodone clearance or hydrocotarnine clearance by Mann-Whitney's U test. Group A included patients whose rest of time to death were 8 d or more, no liver metastasis or no heart failure. And group B included patients who were

Fig. 4. Relationship between Oxycodone Clearance or Hydrocotarnine Clearance and Age

There was good correlation between oxycodone clearance and age ($r=0.666$). There was no correlation between hydrocotarnine clearance and age ($r=0.216$). Symbol: $\circ$, patients who were within 7 d on the death, liver metastasis or heart failure; $\bullet$, patients whose rest of time to death were 8 d or more, no liver metastasis or no heart failure.

within 7 d on the death, liver metastasis or heart failure. As a result, the oxycodone clearance of group A and B were respectively 43.9 ± 27.2 (mean $\pm$ S.D.) and 20.4 ± 8.8 . While hydrocotarnine clearance of group A and B were respectively 119.4 ± 64.4 and 50.6 ± 35.1 . The mean clearance of oxycodone and hydrocotarnine were about twice in group A compared with B, and were statistically significant (oxycodone: $p=0.035$, hydrocotarnine: $p=0.044$, Fig. 3). And there was good correlation between oxycodone clearance and age ($r=0.666$, Fig. 4). But there was no correlation between hydrocotarnine clearance and age ($r=0.216$, Fig. 4).

DISCUSSION

The compound injections of oxycodone and hydrocotarnine contains 8 mg of oxycodone hydrochloride and 2 mg of hydrocotarnine hydrochloride. Hydrocotarnine is a non-narcotic opium alkaloid discovered in 1871. The pharmacologic action belongs to the codeine, and it has an analgesic effect, respiratory depressant effect, anesthetizing effect, and stiffening convulsion appearance effect in the laboratory animal.⁴⁾ It is reported that hydrocotarnine is added to reinforce the action of oxycodone,⁵⁾ but the effect of hydrocotarnine is uncertain and no report contains any evidence of this. Oxycodone is the most commonly used opioid among analgesics for the relief of moderate-to-severe pain and is a mu and kappa opioid receptor agonist.^{6,7)} It was synthesized as a half synthetic conductor of tebain, a natural alkaloid, in 1916. Compared with morphine, the analgesic effect is just as good or 2/3 as good,⁸⁾ the adverse effects are just as bad,⁹⁾ and delirium and nausea/vomiting episodes are fewer.^{9,10)} Oxycodone is metabolized mostly in the liver and oxymorphone, the metabolite of oxycodone metabolized by CYP2D6,¹¹⁾ is pharmacologically active.¹²⁻¹⁴⁾ However, it is thought that oxymorphone has no particular influence on the analgesic effect and the side effects of oxycodone because it is an ultra small amount.¹⁵⁾ In this study, the pharmacokinetic parameters of oxycodone and hydrocotarnine were calculated and determined for the mobilizing factor of drug clearance to design a detailed dosage for each condition. As a result, oxycodone pharmacokinetic parameters were calculated as follows: $CL=37.91/\text{h}$, $V_d=226.71$. Compared with the value reported in other countries (CL ; 46.8 l/h, V_d ; 2.6 l/kg),¹⁶⁾ CL showed a low value and V_d showed a high value. Oxycodone clearance was low in our patients with cancer pain. Cancer

patients generally have a decreased vital function and often have a different level of metabolic enzyme expression in the liver. The low clearance observed may be accounted for by delayed elimination of the drug associated with cancer patients' poor health condition. In contrast, V_d was high; it was probably due to changes in the distribution volume of oxycodone in tissues which was caused by edema and loss of body fat occurring secondary to cancer. And in our study, hydrocotarnine pharmacokinetic parameters were calculated for the first time in the world. CL and V_d of hydrocotarnine are higher than those of oxycodone and each value is as follows: $CL=95.1$ l/h, $V_d=276.8$ l.

The clearance of oxycodone represented by a regression formula was significantly correlated to the age, the presence or absence of within 7 d on the death or liver metastasis, or of the heart failure of the patients. Approximately 80% of oxycodone is metabolized by the liver *in vivo* and 20% is excreted from the kidneys as an unchanged drug.¹⁷⁾ One of the impediments that reduces oxycodone clearance is aging, which causes a decrease in renal and hepatic functions. Oxycodone clearance may also be considerably altered with changes in liver blood flow because of the high clearance of 46.8 l/h (=780 ml/min),¹⁶⁾ and accordingly it is expected to decrease when hepatic blood flow is impaired. However, taking account of the high bioavailability of 60%¹⁸⁾ and 87%,¹⁹⁾ the oxycodone clearance, a metabolized amount of oxycodone, is overestimated and unlikely to be that large. Furthermore, changes in liver metabolic enzyme activity can have some effects on oxycodone clearance. Taken together, it seems that the lack of hepatic blood flow and low metabolic enzyme activity significantly decreased oxycodone clearance of cases with fatal outcome within 7 d and those with liver metastasis or heart failure. Tallgren M. *et al.*²⁰⁾ reported that the mean elimination half-life shortened from 13.9 to 3.4 h in liver transplant patients treated with intravenous oxycodone before and after transplantation. This is consistent with our results and suggests hepatic metabolism has influence on oxycodone clearance to some degree. Factors influencing hydrocotarnine clearance were investigated using the same predicting factors as oxycodone because there was no pharmacokinetic data and its elimination site was unknown. As a result, within 7 d on the death and the presence or absence of liver metastasis or heart failure, were found to be significant factors for fluctuation. Since the hydrocotarnine clearance was estimated as high as mean 95.1 l/h (=1585 ml/min) in this study, changes in liver blood flow may alter the clearance.

In this study, we calculated the oxycodone and hydrocotarnine pharmacokinetic parameters of patients with cancer pain to whom the compound injections of oxycodone and hydrocotarnine was administered. As this is the first time the parameters of hydrocotarnine have been calculated, this critical data will contribute to the estimation of the serum concentration and the pharmacokinetics of hydrocotarnine in the future. And as it was suggested that the high serum concentration level of oxycodone and hydrocotarnine might be observed in geriatric patients or in the condition of hepatic blood flow decreasence, it is necessary to regard dose adjustment for those patients, for example, the administration of a lesser dosage.

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