[**Original Research**]

The Effect of Oral Methadone on the QTc Interval and Pain in Japanese Patients with Cancer Pain

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Abstract: Methadone tablets were approved for use in Japan in March 2013, and have used as a strong opioid for the WHO 3-step ladder to treat cancer pain. However, methadone may have severe adverse effects such as respiratory depression and QT prolongation, and it must be used with caution. In this study, we investigated whether methadone blood concentration and dosage affect severe adverse effects and analgesic effects in Japanese cancer pain patients using methadone. Twenty-four patients were enrolled into this study. It was observed that VAS decreased significantly with increasing blood concentration ($p < 0.0001$). The mean QTc after methadone administration was not significantly changed. In addition, there was no significant increase in QTc with the increase in blood methadone concentration ($r = 0.166$, $p = 0.380$). Also, there was no significant increase in QTc and QTc change rate with increasing cumulative methadone dose ($r = 0.153$, $p = 0.363$, and $r = 0.259$, $p = 0.244$). No patients had increased nausea or vomiting after the start of methadone, but one patient had a respiratory rate of 10 or less per minute. Oral methadone provided a rapid analgesic effect, and severe adverse effects such as respiratory depression and QT prolongation were rare. In addition, QTc did not correlate with blood concentration and dose of methadone.

Key words: methadone, QT prolongation, cancer pain, respiratory rate, adverse effects

INTRODUCTION

Methadone tablets were approved for use in Japan in March 2013. Methadone is a diphenylheptane derivative, first synthesized in Germany in 1937, and is currently used all over the world. The analgesic effects of methadone are attributed to its agonism of μ-opioid receptors and inhibition of *N*-methyl-D-aspartate (NMDA) receptors,[1–3] and it is used as a strong opioid for the WHO 3-step ladder to treat cancer pain.[4] However, methadone may have severe adverse effects such as respiratory depression and QT prolongation, and its use must be done with caution. In a case report, respiratory depression was caused by the combined use of fluconazole with CYP3A4 inhibition.[5] In another case report, conversion of hydromorphone to high doses of methadone caused respiratory depression.[6] In reports of QT prolongation, some reports show that methadone dose and blood concentration correlate with QT prolongation,[7, 8] but some reports do not.[9–12] In addition, a case report showed a QTc of 510 ms with high dose methadone combined with the CYP3A4 inhibitor itraconazole.[13] Thus, respiratory depression and QT prolongation of methadone may affect methadone dose and blood levels, but there is no clear evidence. Furthermore, in Japanese patients with cancer pain, there have been few reports examining the severe adverse effects and the analgesic effect of methadone.

Therefore, in this study, we investigated whether methadone blood concentration and dosage affect severe adverse effects and analgesic effects in Japanese cancer pain patients using methadone.

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MATERIALS AND METHODS

1. Subjects

The Institutional Review Board at KKR Sapporo Medical Center (August 2015 to August 2018) and Itami Hospital (January 2018 to August 2018) approved this study. Patients were eligible if they had a diagnosis of cancer, whose age was greater than or equal to 20, had no prior history of methadone use, and were being started on methadone for pain management as a switch from other strong opioids.

The clinical studies were approved by the ethics committees for each site, and the experiments were conducted in compliance with the Declaration of Helsinki. All par-

ticipants provided written informed consent prior to screening.

2. Methods of clinical studies

The analgesic effect, adverse effects, and blood concentration of methadone were confirmed for 10 days after oral methadone initiation. Methadone was administered by switching from other strong opioids, and the conversion ratio and method used were in accordance with those described in the package insert of the methadone formulation, with reference to previous reports.[14–16] That is, 60 to 160 mg/day morphine is equivalent to 15 mg/day methadone, and 160 to 390 mg/day morphine is equivalent to 30 mg/day methadone. The method of switching to methadone was the stop and go (SAG) scenario. The methadone tablet used was Methapain® (Teikoku Seiyaku Co., Ltd.), and the administration was scheduled twice or three times a day depending on the patient's health condition. If the patient experienced pain, rescue administration using other opioids was carried out. The analgesic effect is evaluated by visual analog scale (VAS, 0–100 mm) once a day, and to determine the QTc interval, we obtained 12-lead electrocardiogram (ECG) from subjects at baseline, and at 120–168 h and 192–240 h after methadone initiation. In addition, when nausea, vomiting, or respiratory depression appeared, each instance was recorded. Blood samples were collected for analysis of trough methadone levels on 24 h, 72 h, 144 h, and 216 h after the start of methadone treatment.

3. Determination of methadone in serum

Methadone concentrations in serum samples were determined by high-performance liquid chromatography-electrochemical detector (HPLC/ECD), using a previously developed method.[17] The HPLC/ECD system consisted of an HPLC pump PU-2080 (Nihon Bunko, Tokyo, Japan), an autosampler AS-2059 Plus (Nihon Bunko, Tokyo, Japan), a column oven CO-1560 (Nihon Bunko, Tokyo, Japan), an electrochemical detector Coulochem Ⅲ, and the Analytical cell 5010 (Nippon Dionex, Tokyo, Japan). The analytical column was XTerra® RP18 (5 μm, 4.6 × 50 mm i.d., Waters, Japan). The mobile phase was 10 mM Na_2HPO_4/CH_3CN/CH_3OH (20:19:3). The flow rate was 1.0 mL/min, and the total run time was 5 min. The voltage of the electrochemical detector was set at 400–800 mV. After collection, the blood samples were immediately centrifuged at 3000 rpm for 10 min. To 1.0 mL of the serum samples (standard and test), 0.5 mL 4 N NaOH and 4 mL butyl chloride were added. Then, the samples were mixed and centrifuged for 10 min at 3000 rpm; next, the butyl chloride (top layer) was harvested and transferred into a clean glass tube. The butyl chloride extract was then evaporated. The dried residue was reconstituted in 200 μL of the mobile phase, and 40 μL of this solution was injected into the HPLC system for analysis.

4. Analgesic effect and adverse effects of methadone

The analgesic effect was evaluated by VAS, and the relationship between VAS and methadone dose or blood concentration was examined. QT prolongation was evaluated by QTc, and changes in QTc at baseline, and at 120–168 h and 192–240 h after methadone initiation were observed. Correlation analysis was also performed between QTc and methadone dose or blood trough concentration. Analysis of variance (ANOVA) was performed on the analgesic effect (VAS), blood methadone concentration, and QTc after administration of methadone. Also, Correlation between QTc and methadone dose and blood trough concentration were analyzed using Pearson correlation coefficient. A two-sided p value of less than 0.05 was considered to be statistically significant. In addition, if nausea or vomiting increased after the start of methadone, it was recorded. Respiratory rate per minute was also recorded for patients with a decreasing respiratory rate.

RESULTS

1. Patient characteristics

Table 1 highlights the characteristics of patients included in this study. Twenty-four patients were enrolled into the study. Eleven females and 13 males were enrolled, and their age ranged from 39 to 81. The methadone dose was 5–75 mg/day (median: 15 mg/day), which was a low dose. During the study period after switching to methadone, there were no changes, additions, or discontinuations of concomitant medications that would affect analgesic effects and side effects.

2. Analgesic effect on methadone dose and blood level

Figure 1 (a) shows the change in methadone dose in each case after methadone administration. Figure 1 (b) shows the time course of blood trough concentration after methadone initiation. Figure 1 (c) shows the analgesic effect (VAS) over time after methadone initiation. The blood methadone concentration showed a significant increase over time after methadone initiation ($p<0.0001$). In addition, a significant decrease in the analgesic effect (VAS) was observed ($p<0.0001$).

3. Adverse effects on methadone dose and blood level

Figure 2 shows the changes in QTc before methadone administration and 120–168 h and 192–240 h after administration. The average QTc was 0.428 s, 0.441 s, and 0.436 s, respectively, and there was no significant change ($p=0.3402$). However, in case 18 only, QTc transiently became 0.51 s and showed an abnormal value. The dose of methadone in case 18 was 25–30 mg/day, and the blood concentration was not high at 45.5 ng/mL, 109.5 ng/mL, and 115.6 ng/mL at 48, 120, and 216 h, respectively. Also, her cardiac function was in the normal range, and it was unclear why QTc was prolonged.

Figure 3 shows the relationship between blood methadone concentration and QTc. There was no significant increase in QTc with the increase in blood methadone concentration ($r=0.166$, $p=0.380$). Figure 4 (a) and (b) show the relationship between cumulative methadone dose and QTc or QTc change rate. There was no signifi-

Table 1 Patient characteristics

Patient No.	Primary disease	Gender	Age	BW (kg)	Methadone dose (mg/day)	eGFR (mL/min/ 1.73 cm)	T-Bil (mg/dL)
1	Lung cancer	F	73	39.2	10–15	82.1	0.6
2	Malignant pleurisy mesothelioma	F	81	60.9	15	64.2	0.3
3	Ovarian cancer	F	56	47.1	15–45	89.1	0.3
4	Gastric cancer	M	63	55.6	15–20	74.4	0.2
5	Lung cancer	M	52	48.4	15–45	85.5	0.3
6	Lung cancer	M	44	66.9	5	100.5	0.3
7	Breast cancer	F	48	85.1	15	59.1	2.4
8	Lung cancer	M	55	65.2	15	88.0	0.3
9	Cervical cancer	F	39	40.0	30–75	36.1	0.2
10	Bile duct cancer	M	60	60.1	15–35	87.1	2.4
11	Lung cancer	F	49	43.8	5–15	82.0	0.3
12	Lung cancer	M	68	57.1	10	65.1	0.4
13	Liver cancer	M	68	72.3	10	50.3	0.3
14	Lung cancer	M	72	65.6	15	81.4	0.6
15	Lung cancer	M	73	42.4	5–10	129.3	0.9
16	Breast cancer	F	69	43.0	10–15	119.1	0.4
17	Lung cancer	M	58	58.9	10	80.9	0.4
18	Ovarian cystoma	F	69	48.4	25–30	101.9	0.4
19	Lung cancer	F	64	44.7	15	70.8	0.3
20	Lung cancer	M	62	60.0	10–15	87.7	0.5
21	Lung cancer	M	79	47.5	15	74.7	0.8
22	Lung cancer	M	60	73.0	20	62.6	0.6
23	Gastric cancer	F	40	40.0	15–25	112.8	0.6
24	Colon cancer	F	50	50.0	10–15	59.1	0.4
Mean			60.5	54.8	19.8	77.8	0.6
Median			61.0	52.8	15	81.7	0.4
SD			11.5	12.0	13.7	21.2	0.6
Minimum			39	39.2	5	36.1	0.2
Maximum			81	85.1	75	129.3	2.4

BW: body weight, eGFR: estimated glomerular filtration rate = $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ (if female, $\times 0.739$).

cant increase in QTc and QTc change rate with increasing cumulative methadone dose ($r=0.153$, $p=0.363$, and $r=0.259$, $p=0.244$).

In addition, no patients had increased nausea or vomiting after the start of methadone administration. Furthermore, the respiratory rate per minute after the start of methadone administration in patients whose respiratory status was observed is shown in Fig. 5. In case 6 only, the respiratory rate per minute became 10 or less after the start of methadone. The dose of methadone in case 6 was 5 mg/day, and the blood concentration was not high at 10.8 ng/mL, 37.1 ng/mL, and 37.8 ng/mL at 24, 72, and 144 h, respectively. But this patient had lung cancer.

DISCUSSION

In this study, we observed changes in blood concentration of methadone, analgesic effects, and side effects after using oral methadone in patients with cancer pain. We also clarified the relationship between blood methadone concentration and dose and analgesic effect or adverse effect.

After the administration of methadone, the blood methadone concentration gradually increased, and the pain (VAS) significantly decreased accordingly (Fig.1 (b), (c)). In the report by Ventafridda et al.[18], a clear reduction in the intensity of the pain can be seen over the first 2 days of treatment, followed by a constant control of pain during the remaining period. In addition, in a report targeting Japanese cancer patients, it was reported that the mean NRS (Numeric Rating Scale) significantly decreased from 7.5 to 2.8 after administration of methadone.[19] These reports are similar to our results.

In addition, Fig. 2 shows changes in QTc after administration of methadone, and there was no significant change in QTc at 120–168 h and 192–240 h after administration as compared with before administration of methadone. However, in case 18 only, the QTc was transiently increased, but the QTc was recovered without the reduction of methadone. In this case, the cardiac function was normal, the dose and blood concentration were not high, and it was unknown why the QTc increased. In addition, Fig. 3 shows the relationship between blood trough concentration and QTc, and there was no significant correlation. Furthermore, Fig. 4 (a) and (b) show the relationship between the cumulative dose of methadone and QTc, and there was no significant correlation between QTc and QTc change rate. There are two groups of conflicting reports regarding methadone: one that states its doses or blood levels are correlated

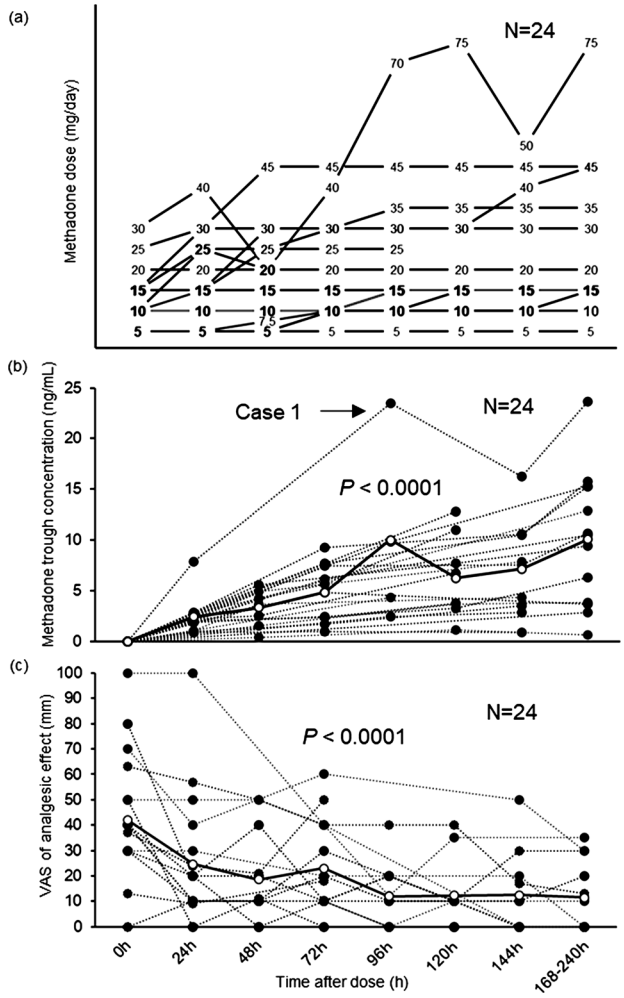

Fig. 1 Changes in methadone dose (a), methadone blood level (b), and analgesic effect (c) after starting methadone. White circles and solid lines show mean values.

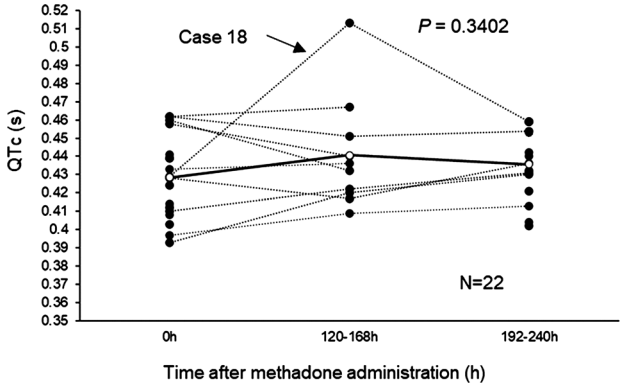

Fig. 2 Changes in QTc after methadone administration. White dots and solid lines show mean values. Case 18 is a case in which a transient increase in QTc was observed.

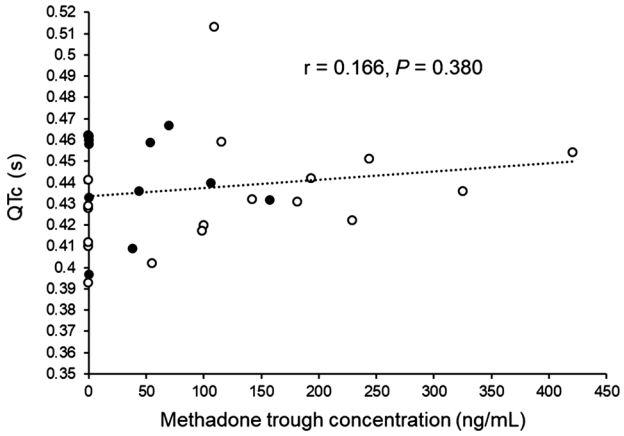

Fig. 3 Relationship between methadone trough concentration and QTc (white dots; female, black dots; male). The trough concentration in the figure is the most recent value at the time of QTc measurement.

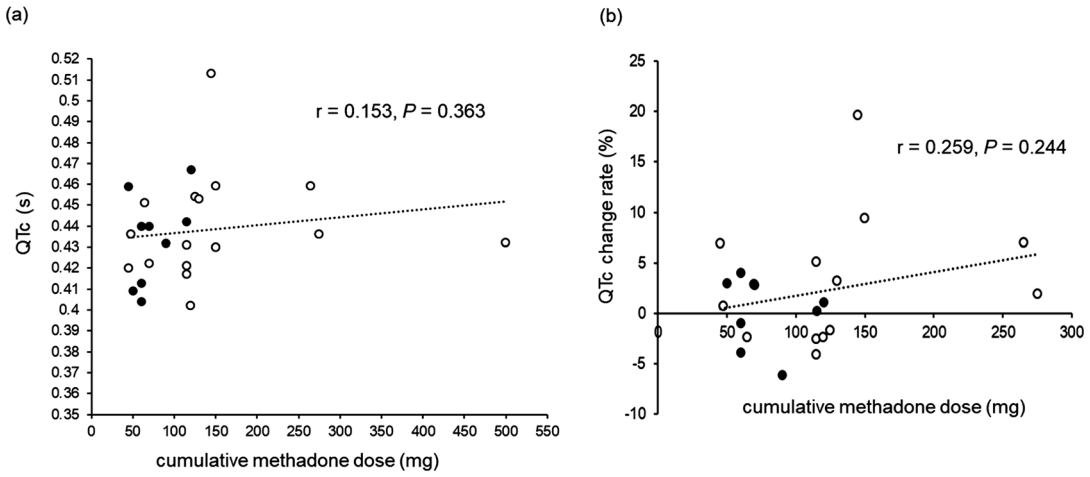

Fig. 4 Relationship between cumulative methadone dose and QTc (white dots; female, black dots; male).

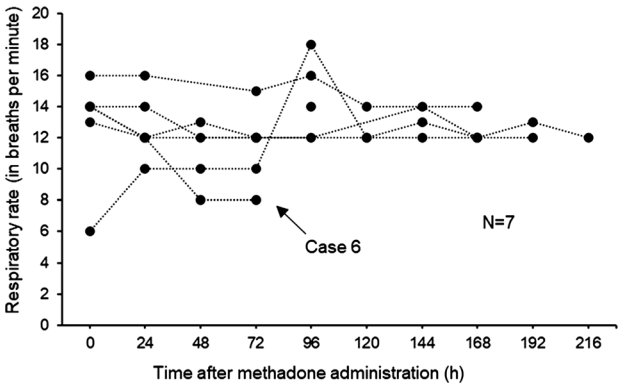

Fig. 5 Change in respiratory rate per minute after methadone administration. Case 6 is a case in which the respiratory rate per minute decreased to 10 times or less.

with QT prolongation,[7, 8] and the other that states they are not correlated.[9–12] The mean or median doses of methadone in studies with reference numbers 7 and 8 were high (145 mg/day and 397 mg/day, respectively), whereas those with reference numbers 9–12 were low (30 mg/day, 53 mg/day, 80.4 mg/day, and ≤ 60 mg/day, respectively). This difference in dosages is considered to have caused the differences in correlations between methadone dose and QT prolongation. In our study, since the median dose of methadone was low (15 mg/day), our results did not correlate with QT prolongation.

Figure 5 shows the changes in the respiratory rate for 1 min after the administration of methadone in the patients whose respiratory rate was measured. In case 6 only, the respiratory rate was less than 10. This patient had lung cancer and had poor respiratory function, so the dose of methadone was carefully given at 5 mg/day. Thus, it was considered necessary to carefully monitor the administration of methadone to patients with weak respiratory function.

Methadone is mostly metabolized in the liver. Therefore, when liver function is lowered, the blood level of methadone as well as its pharmacological activity may be elevated. However, in patients 4 and 10, who showed high levels of bilirubin, adverse reactions, such as QT prolongation and respiratory depression, did not occur; this may be explained by the fact that the dose of methadone was low and the study period was short (10 days). In addition, in patient 9, whose renal function was reduced, adverse reactions including QT prolongation and respiratory depression did not occur.

The limitation of this study is that our sample size was small (24 patients) because our study was limited to those in whom blood levels of methadone were measured. However, we were able to analyze, according to age and renal and liver function, a wide range of patients presenting with cancer pain, which roughly represents the patient population using methadone. Thus, this study appears to provide useful information regarding the clinical use of methadone.

In this study, we clarified the relationship between blood methadone concentration and dose, analgesic effect, and adverse effects in Japanese patients with cancer pain. Oral methadone exerted a rapid analgesic effect, and severe adverse effects such as respiratory depression and QT prolongation were rare. However, if cardiac and respiratory function decline, it may be necessary to start with a low dose of methadone and carefully monitor it. Since this study does not have enough cases, it is necessary to accumulate many cases in the future.

Conflict of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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