学位論文

Response to intravenous fentanyl infusion predicts subsequent response to transdermal fentanyl

（慢性痛患者におけるフェンタニルの点滴と貼付の相関）

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著者の宣言

学位論文は、著者の責任において研究を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

ABSTRACT

Purpose.

Prediction of the response to transdermal fentanyl (FENtd) before its use for chronic pain is desirable. We tested the hypothesis that the response to intravenous fentanyl infusion (FENiv) can predict the response to FENtd, including the analgesic and adverse effects.

Methods.

The study subjects were 70 consecutive patients with chronic pain. The response to fentanyl at 0.1 mg diluted in 50 ml of physiological saline and infused over 30 min was tested. This was followed by treatment with FENtd (Durotep MT patch 2.1 mg®) at a dose of 12.5 μg/hr for 2 weeks. Pain intensity before and after FENiv and 2 weeks after FENtd, and the response to treatment, were assessed by the numerical rating scale (NRS), clinical global impression-improvement scale (CGI-I), satisfaction scale (SS), and adverse effects.

Results.

The NRS score decreased significantly from 7 (4-9) [median (range)] at baseline to 3 (0-8) after FENiv ($P<0.001$), and to 4 (1-8) after FENtd ($P<0.001$). The effects of FENiv, as evaluated by ΔNRS, CGI-I, and SS, were significantly greater than those of FENtd ($P<0.001$, each), but not by the frequency and the severity of adverse effects, with the exception of dizziness. ΔNRS, and severity of adverse effects (drowsiness, dizziness, nausea, dry mouth, and pruritus) of FENiv correlated significantly with those of FENtd ($rs>0.04$, each).

Conclusions.

The analgesic and side effects after intravenous fentanyl infusion can be used to predict the response to short-term transdermal treatment with fentanyl.

Contents

1. Introduction

The use of opioids for treatment of chronic pain is increasing exponentially[1]. Potent opioids are used as an option for patients with refractory chronic pain, but not all patients respond satisfactorily to this treatment. Prediction of responders to potent opioids therapy is desirable, in order to avoid exposure of non-responders to the harmful and adverse effects of these compounds.

Intravenous analgesic infusion tests have been used in a variety of contexts for almost 20 years to delineate pain mechanisms and predict response to oral or transdermal analogues[2]. Dellemijin et al.[3][4] reported in two separate studies that intravenous fentanyl infusion (FENiv) test can help identify patients with chronic pain who might benefit from long-term treatment with transdermal fentanyl (FENtd). In this test, a potent opioid, fentanyl, is infused at a rate of 5 μg/kg/hr for maximum of 5 hr, with a mean infusion dose of 873 μg (95%CI 743-1004 μg). One problem with this test is that the infusion dose can potentially cause serious complications, such as dizziness, drowsiness, sleepiness or apnea. In addition, the time period between FENiv and FENtd as well as the doses of FENiv and FENtd are not controlled in the test. Therefore, an alternative FENiv test is needed to predict the safety and response of FENtd in which a lesser and tolerable dose of fentanyl is used in the outpatient setting. Moreover, the fixed dose, 12.5 μg/hr of FENtd in many countries, must be started for chronic pain patients regardless of their body weight. The simple FENiv test is desirable, which can be carried conveniently and used by anyone without miscalculation of the dose.

The purpose of the present study was to examine the predictive effect of 100 μg/30 min of FENiv before the infusion of 12.5 μg/hr of FENtd. The selected dose for FENiv produces double the blood fentanyl concentrations observed during treatment with FENtd. This was established using the simulation software TIVATRAINER™ (Copyright to Frank Engberts, Leiden, The Netherlands). Intravenous infusion of 100 μg of fentanyl over 30 min transiently produced fentanyl blood concentrations equivalent to the maximal blood

concentration after 25 μg/hr of FENtd in patients with body weight of 50 kg. On the other hand, the selected dose for FENtd is the recommended initial dose for FENtd. We investigated whether the response and side effects of transient increase in blood concentration of fentanyl (after intravenous infusion) correlate with those observed after FENtd therapy in patients with chronic pain.

2. Materials and Methods

2-1. Patients

Seventy consecutive patients scheduled to receive FENtd for the treatment of chronic pain at Kitasato University Hospital were enrolled in this study. The study was approved by The Hospital Ethics Committee and informed consent was obtained from all patients. The inclusion criteria for the selection of patients were age from 20 to 85 years, body weight from 30 to 100 kg, pain persisting for more than 3 months, typical pain intensity of ≥4 according to a Numerical Rating Scale (NRS, 0-10 with 10 being the worst pain and 0 being no pain), and capacity for proper assessment of pain severity before and after FENiv. Excluded from the study were patients with severe psychiatric or psychological diseases, serious chronic diseases, such as cardiac failure, pulmonary emphysema, and interstitial hepatitis, skin problems that might affect transdermal delivery, and life-limiting conditions. Also excluded were other patients in whom any opioids therapy was previously continued or oral medications were changed within one week before the study.

2-2. Procedures

After rest in supine position, an intravenous cannula was established in the antecubital vein. Fentanyl (100 μg dissolved with 50 ml of physiological saline) was infused intravenously over a period of 30 min. Between the time of discharge and the night of that day, Durotep MT patch 2.1mg® (Janssen Pharmaceuticals, Inc), which provides 12.5 μg/hr of fentanyl over 72 h was initiated. The same dose was repeated every 72 hrs for two weeks.

Any medication used previously was continued during the study period to avoid reinforced chronic pain. However, patients were allowed to change medication when exquisite pain or adverse events occurred, and were regarded as dropout patients of the trial.

2-3. Outcomes

Blood pressure and pulse rate were measured immediately before and every 5 min during FENiv. Daily pain intensity was assessed using the NRS immediately before and after FENiv, and 14 days after FENtd. In patients with pain on movement, the intensity of pain induced by movement was evaluated. We defined the degree of pain intensity difference (PID) as the baseline pain intensity minus pain intensity after treatment. PID was expressed as a percentage of daily pain intensity. We also measured the Clinical Global Impression - Improvement scale (CGI-I, 1: maximally improved, 2: moderately improved, 3: mildly improved, 4: no change, 5: mildly worse, 6: moderately worse, 7: severely worse) to assess pain improvement or worsening relative to the baseline state[5]. Furthermore, the satisfaction scale (SS, 1: very satisfied, 2: satisfied, 3: neither satisfied nor dissatisfied, 4: dissatisfied, 5: very dissatisfied) was checked to judge patients' impression on treatment. The assessment points of the CGI-I and the SS were similar to those of the NRS but "immediately before FENiv". In the FENtd dropout patients, the NRS, CGI-I and SS were assessed at the point of discontinuation of FENtd.

Adverse events were estimated with 4-points of the Verbal Rating Scale (0: none, 1: slight, 2: moderate, 3: severe). The experienced assessors of outcomes were masked to the contents of drug used in the treatment, and were unaware of the details of patient background.

2-4. Data analysis

Continuous parameters were summarized as median (range), and categorical data were presented as numbers. The NRS score, mean blood pressure, and

pulse rate before and after treatment were assessed by the Wilcoxon Signed-Rank test for nonparametric paired data. For comparison of the effects of FENiv with FENtd on the rate of change of NRS score, CGI-I and SS scores, data were also evaluated using the Wilcoxon Signed-Rank test. Regarding the categorical variables for the distribution of severity of each adverse effect between FENiv and FENtd, m x n Chi square test and Fisher's exact test were used. Furthermore, Spearman's rank correlation was used to examine the correlation between the effects and adverse effects between FENiv and FENtd. Differences were assessed with two-sided tests, with an alpha level of 0.05. Analyses were performed with JMP® Pro Ver. 10.0.2 software (SAS Institute, Inc., Cary, NC).

3. Results

3-1. Patients informations

Seventy consecutive outpatients (43 females, 27 males) with chronic pain were enrolled in the study (Table 1). The cause of pain varied among the subjects, but all reported persistent pain for at least 3 months despite all attempts at pain relief. Ten patients did not complete the 2-week trial of FENtd due to side effects in 7 (5 nausea, 1 drowsiness, and 1 pruritus), insufficient effect (n=2), and improvement of pain (n=1). None developed complications related to FENiv or FENtd, and none was lost to follow-up during the study period, and all patients provided the required follow-up information.

3-2. Analgesic effects

The NRS score decreased significantly from 7 (range, 4-9) at baseline to 3 (0-8) after FENiv (P<0.001), and to 4 (1-8) after FENtd (P<0.001). As shown in Table 2, the effects of FENiv evaluated by PID, CGI-I and SS scores were significantly greater than those of FENtd (P<0.001, each). Changes in PID, CGI-I and SS after FENiv correlated significantly with those after FENtd.

As shown in Figure 1, in patients who showed complete disappearance of

pain after FENiv (PID=100% on the abscissa), the analgesic effect of FENtd varied widely (PID=28.6 to 85.7% on the ordinate). On the other hand, in patients with less than 50% of PID due to FENiv (PID ≤50% on the abscissa), the analgesic effect of FENtd was inadequate (PID ≤50% on the ordinate).

3-3. Adverse effects

There were no significant differences in the frequency and severity of common adverse effects, with the exception of dizziness, between FENiv and FENtd (Table 3). However, the severity of the side effects after FENiv correlated significantly with those encountered after FENtd (Table 3). In this regard, grade 1 constipation was noted in 5 patients following FENtd, although it did not require specific medications.

4. Discussion

4-1. Summarise key results

Our results suggest that the response to intravenous infusion of 100 μg of fentanyl over 30 min can predict the subsequent short-term analgesic effects and side effects of transdermal administration of 12.5 μg/h of fentanyl, commercially available as FENtd 2.1 mg.

Analgesia seems superior with FENiv 100 μg than FENtd 12.5 μg/hr; possibly because the maximum blood concentration of fentanyl after FENiv 100 μg over 30 min is higher than that after FENtd 12.5 μg/hr. The analgesic effect of FENtd 12.5 μg/hr seems insufficient when FENiv 100 μg provides insufficient analgesia, although the effect varies when FENiv 100 μg produces extremely effective analgesia. That the FENiv 100 μg test is clinically meaningful is shown by its ability to predict poor responders to sustained-release formulations.

4-2. Interpretation

Clinical evidence indicates that opioids provide effective short-term pain relief in nearly any type of painful condition[6)7)]. However, in the meta-analysis of Kalso

et al.[8], the number needed to harm was 3-5, in other words, one in 3-5 patients treated with opioids was expected to be exposed to adverse events. This finding highlights the importance of intravenous opioid test for identifying potential responders to subsequent treatment and avoidance of these drugs in non-responders.

Previous studies demonstrated discrepant results regarding the usefulness of intravenous opioid test in predicting subsequent response to oral or transdermal treatment. For example, two studies reported negative predictive values of more than 90%[4)9)]. Another study showed poor correlation between intravenous and continuous release opioid[10)]. Part of the problem with the use of intravenous infusion test to predict the response to sustained-release opioid treatment is that more than 80% of patients cease therapy not because of poor shot-term analgesia, but secondary to adverse effects. In the present study, the predictive value of intravenous fentanyl was evaluated for adverse effects as well as analgesic effects, and the results showed the test can detect common adverse effects. Especially, dizziness and drowsiness showed marked correlation with intravenous and transdermal fentanyl. Opioids use may lead to falls caused by dizziness and drowsiness, particularly in elderly opioids users who are vulnerable to bone fractures and other falls-related painful, debilitating injuries[11)]. Recent studies demonstrated increased risk of fall-related injuries associated with new prescriptions of opioids, especially during the first week of opioids treatment[12)]. Therefore, it is important to predict the likelihood of dizziness and drowsiness in the early stage of opioids use. The most advantageous utility of FENiv test is the ability to predict high responders with adverse effects to FENtd therapy.

In the present study, there was some discrepancy in response between FENiv and FENtd, since both administration routes provided the same opioid, fentanyl. The maximum blood fentanyl concentration in FENtd is difficult to be estimated in each patient because of luck of a simulation software, although that in FENiv is calculated to be 1.49 (0.85-2.26) ng/ml in patients with 63 (26-

83) years of age , 56 (37-98) kg of body weight ,and 160 (133-182) cm using Anest Assist PK/PD. The patient skin condition including local temperature may affect the dermal penetration of fentanyl and the consequent analgesia and side effects. Also, patients received FENiv for a short period at rest, whereas used FENtd all day long while moving and eating. The intravenous test cannot take into account the influence of patient's life and environment. The difference in patient state may cause the discrepancy in response to the same fentanyl.

Before treatment with FENtd, a fixed-term opioids trial is sometimes recommended. Weak opioids, such as codeine and tramadol, are commonly used to test the efficacy and tolerability of FENtd. However, codeine and tramadol are prodrugs of opioids, and are bioactivated by CYP2D6 into morphine and M1, respectively. Interindividual variability in the metabolism and response to these drugs exists. These drugs are ineffective at the usual clinical doses in 7 to 10% of Caucasians because of homozygosity for nonfunctional mutant CYP2D6 alleles[13]. Conversely, among individuals with duplicated or amplified active CYP2D6 genes who are classified as having ultrarapid metabolism, the intake of codeine or tramadol may result in higher opioids production, causing life-threatening intoxication[14]. Considering the potential of both lack of therapeutic effect and life-threatening adverse reactions, in addition to the difference in the function of morphine, M1 and fentanyl, it is difficult to substitute codeine or tramadol for fentanyl in FENtd titration.

Care should be exercised when interpreting the results of the FENiv test. First, pain should be induced while the subject is moving before and after FENiv since patients report pain mainly while moving, rather than during rest. Second, the test should be performed at constant room temperature since changes in this variable could alter blood flow or sympathetic tone, which in turn could change pain intensity[15]. Third, ant placebo effect of FENiv must be taken into consideration especially in patients with chronic pain and psychopathology[16]. Drip infusion of saline as placebo prior to FENiv, and differences in reaction to

saline and FEN infusion should be assessed to determine the true efficacy of fentanyl.

4-3. Limitation

The present study has certain limitations. In this study, medications used by the patients were not discontinued during the study period to avoid reinforced chronic pain. Therefore, the results cannot rule out possible interaction between fentanyl and other medications. In addition, the results were based on data collected with FENtd dose of 2.1 mg. Further analysis of the response to other doses of FENtd is necessary especially in patients under treatment with FENtd. Finally, since no control group was included in the study, no definite conclusions on the predictive value of the FENiv can be made. A randomized placebo-controlled trial is needed to deal with the above shortcomings.

5. Conclusion

The present open-label study on intravenous fentanyl test provided evidence that assessment of the analgesic and adverse effects following intravenous infusion of fentanyl could be potentially useful for the prediction of short-term treatment of chronic pain with transdermal fentanyl.

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Table 1. Patient characteristics

Female : male	43 : 27
Age (years)	63 (26-83)
Height (cm)	160 (133-182)
Body weight (kg)	56 (37-98)
Pain condition	
spondylosis deformans	14
post-herpetic neuralgia	10
post-traumatic neuropathy	9
spinal canal stenosis	8
disk herniation	8
complex regional pain syndrome	4
post-stroke pain	4
chronic arterial obstruction	4
Fibromyalgia	3
osteoarthritis of the knee	2
systemic lupus erythematosus	1
systemic amyloidosis	1
diabetic neuropathy	1
pyogenic spondylitis	1

Data are number of patients or median (range) values.

Table 2. Comparison of effects of FENiv and FENtd.

	FENiv	FENtd*	Comparison of incidence *P* value	Degree of correlation rs
PID (%)	58.6 (0-100)	40.0 (0-87.5)	<0.001	0.591
CGI-I	1 (1-3)	2 (1-4)	<0.001	0.540
1	37	12		
2	27	45		
3	6	9		
4	0	4		
5	0	0		
6	0	0		
7	0	0		
SS	1 (1-3)	1 (1-5)	<0.001	0.502
1	54	41		
2	13	14		
3	3	11		
4	0	3		
5	0	1		

Data are median (range).

PID (%) = (pre NRS score – post NRS score) / pre NRS score x 100

* Data represent the latest scores in the 2-week period of FENtd therapy.

FENiv: intravenous fentanyl infusion, FENtd: transdermal fentanyl, PID: pain intensity difference, CGI-I: clinical global impression - Improvement scale, SS: satisfaction scale.

Table 3. Comparison of adverse effects of FENiv and FENtd.

	FENiv	FENtd*	Comparison of incidence *P* value	Degree of correlation rs
Drowsiness				
0	36	38	0.901	0.645
1	17	18		
2	7	8		
3	10	6		
Dizziness			0.704	0.863
0	58	61		
1	6	8		
2	2	0		
3	4	1		
Nausea			0.923	0.456
0	59	56		
1	6	7		
2	2	1		
3	3	6		
Dry mouth			0.912	0.497
0	69	66		
1	0	2		
2	0	0		
3	1	2		
Pruritus			0.999	0.563
0	69	67		
1	1	2		
2	0	0		
3	0	1		

* Data represent the latest scores in the 2-week period of FENtd therapy.
Abbreviations as in Table 2.

Figure 1

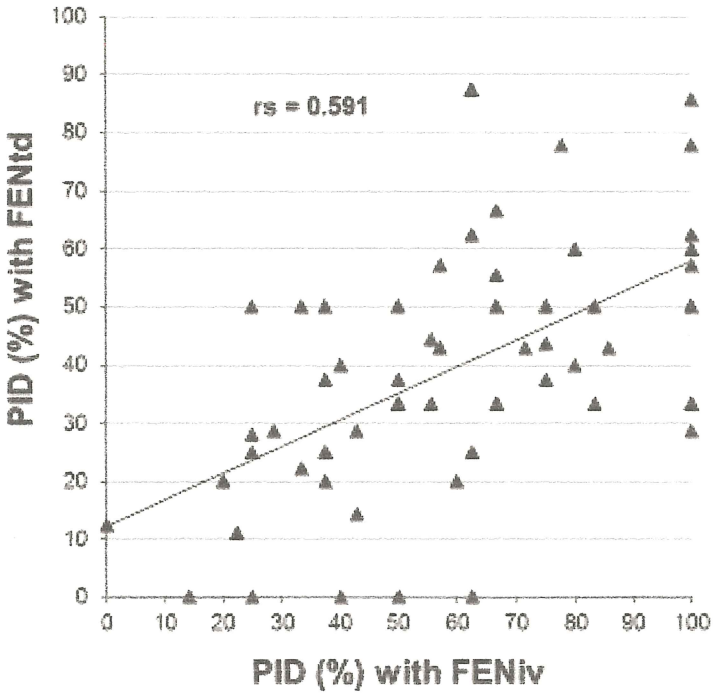

Figure 1: Pain relief with intravenous fentanyl infusion (FENiv) test versus transdermal fentanyl (FENtd). Data of 70 patients.
PID: pain intensity difference.