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Original

Comparison of User Impressions of Oral Transmucosal Fentanyl Placebo Formulations by Medical Staff

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Abstract: Two oral transmucosal fentanyl formulations have been approved in Japan, a buccal tablet and a sublingual tablet. Both these dosage forms take effect rapidly and can be used for patients with cancer-related pain who have difficulty swallowing and taking oral medications; however, few patients have used these formulations, and suitable patient education by medical staff is needed. In addition, rapid-onset opioids might not reach their efficacy potential if administered improperly, and understanding individual patient needs with regard to treatment could affect subsequent evaluations of efficacy. Thus, the treating staff must work with their patients to maximize the proper use of such medicines. In our experience, the sublingual (S) tablet disintegrated in less than 1 minute, while the buccal (B) tablet took considerably longer, about 14 minutes. Moreover, the S tablet was easier to handle, had more favorable user impressions, and had little scattering in the disintegration time, all of which are clinically useful features. We collected further information that would be valuable for patient education, including tablet size and ease of opening the sheet (package) and removing the tablet. Furthermore, to promote proper use of the tablet by the patient, we explain the standard timing of the drug's effectiveness, the need for proper handling of the drug, and attributes such as flavor, to minimize patient anxiety. The user impressions obtained in this study along with knowledge of product characteristics will improve patient education by medical staff and thus promote the medicines' proper use.

Key words: fentanyl citrate, oral transmucosal administration, sublingual tablet, buccal tablet, proper use

Introduction

The treatment of cancer-related pain is conducted through the use of non-steroidal anti-inflammatory drugs and opioid analgesics in accordance with the three-step pain relief ladder of the World Health Organization (WHO) Cancer Pain Relief Programme[1]. Concomitant use of an analgesic adjuvant might also be considered depending on the degree and type of pain. Opioid analgesics used in Japan are mainly classified either as drugs for routine use or as rescue

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formulations. The choices in fentanyl rescue formulations for cancer-related breakthrough pain increased in 2013 when buccal and sublingual tablets of transmucosal immediate-release fentanyl (TIRF) arrived on the market.

Buccal and sublingual tablets are formulations that disintegrate rapidly in the mouth for absorption by the oral mucosa. Unlike short-acting opioids (SAOs) such as morphine hydrochloride and oxycodone hydrochloride that have been used for rescue in the past, the buccal and sublingual formulations are called rapid-onset opioids (ROOs). These agents are rapidly absorbed via the oral mucosa and take effect quickly, making them useful for treating cancer-related pain in patients who have difficulty swallowing and taking oral medications. These formulations have recently appeared on the market and have been used in only a few patients to date ; their proper use is therefore dependent on adequate patient education by medical staff.

Additional types of ROO formulations, such as a candy type transmucosal formulation and a transnasal spray product, have been developed and marketed in foreign countries, and reports have been published on their usefulness in breakthrough pain[2,3]. In addition, patient satisfaction surveys have compared some of the dosage forms to previously used rescue formulations, with the sublingual tablets reported to be favorable with regard to ease of use and palatability[4,5].

In Japan, pharmacists have reported on ROO formulation properties and survey results on user impressions among medical staff (pharmacists) and non-medical staff[6]. However, no study has addressed the content needed for patient education by medical staff other than pharmacists, and many other health professionals are involved when patients use medicines. Clearly, the clinical efficacy of ROO formulation requires its proper use.

The present study aimed to inform patient education about ROO use and efficacy by comparing the ease of use of TIRF with different routes of administration that are on the market in Japan. Necessary information was collected, such as disintegration time, user impressions, sensations during use, and flavor, factors that cannot be gleaned from package inserts or summaries of product characteristics. This information should then improve the selection of a formulation in a clinical setting and the content needed for patient education by medical staff.

Subjects and methods

This study included 40 healthy adult employees of Showa University Hospital [physicians, nurses, pharmacists, and clinical research coordinators (CRCs) / administrative personnel].

A survey study involving 13 items (disintegration time, convenience, palatability, overall impression, etc.) was conducted among the subjects using placebo buccal tablets (B tablet : diameter 6.4 mm, no active ingredient) and placebo sublingual tablets (S tablet : diameter 6.0 mm, no active ingredient). The tablet manufacturers donated all stocks used in this study for research purposes.

The subjects received an explanation of the purpose and method of the study, and those who gave written, informed consent were enrolled as subjects. Persons who were not employees of the hospital or who had experience using either a B tablet or an S tablet prior to the survey were excluded.

This survey was conducted with reference to previous studies in other countries[4]. The survey

covered the following 13 items : occupation ; sex ; age ; disintegration time ; tablet size ; ease of opening the sheet (package) and removing the tablet ; ease of holding the tablet ; ease of using the tablet oneself ; ease of use of tablet by another person (nurse or carer of patients who needed help using the formulation) ; palatability (flavor, effervescence) ; overall impression of using the tablet by the user ; overall impression of use of tablet by another person ; and other (free-text comments) (Table 1).

Table 1. User impression survey of oral transmucosal fentanyl placebo formulations (buccal tablet and sublingual tablet)

Occupation		Physicians Nurses Pharmacists CRCs/Administrative personnel
Sex		Male Female
Age		years
Disintegration time	B tablet (1 tablet)	min sec
	S tablet (1 tablet)	min sec
Size	B tablet	Small Large 0 1 2 3 4 5
	S tablet	Small Large 0 1 2 3 4 5
Ease of opening the sheet (package) and removing the tablet	B tablet	Difficult Easy to remove 0 1 2 3 4 5
	S tablet	Difficult Easy to remove 0 1 2 3 4 5
Ease of holding	B tablet	Difficult Easy to handle 0 1 2 3 4 5
	S tablet	Difficult Easy to handle 0 1 2 3 4 5
Ease of use (patient)	B tablet	Difficult Easy to use 0 1 2 3 4 5
	S tablet	Difficult Easy to use 0 1 2 3 4 5
Ease of tablet use (another person)	B tablet	Difficult Easy to use 0 1 2 3 4 5
	S tablet	Difficult Easy to use 0 1 2 3 4 5
Palatability (flavor, effervescence)	B tablet	Poor Good 0 1 2 3 4 5
	S tablet	Poor Good 0 1 2 3 4 5
Overall impression of tablet use by patient	B tablet	Poor Good 0 1 2 3 4 5
	S tablet	Poor Good 0 1 2 3 4 5
Overall impression of tablet use by another person	B tablet	Poor Good 0 1 2 3 4 5
	S tablet	Poor Good 0 1 2 3 4 5
Other		Please provide any additional thoughts or opinions.

B tablet : placebo buccal tablet ; S tablet : placebo sublingual tablet ; CRCs, clinical research coordinators.

Before any tablet use, a pharmacist explained the location of use (buccal or sublingual) and other key points. The B tablet was to be placed between the cheek and the gum of the maxillary molars, and was not to be chewed or licked. The S tablet was to be placed sublingually at the rear of the tongue and not to be swallowed, licked, or chewed. The tablet was then placed in the proper location, the disintegration time either in the cheek or under the tongue was noted by each subject using a stopwatch, and the median values were compared by occupation.

With the exception of sex, age, occupation, and disintegration time, the survey items were evaluated on a 6-step Likert-type scale, with 5 representing extremely positive and 0 representing extremely negative. The scores were computed, and the mean ± SD values were compared between formulations. In response to "Other (free-text comments)", the subjects entered free-text comments of their impressions after use.

The disintegration times per tablet are expressed as median values as appropriate. The Kruskal-Wallis test was used to examine the significance of values by occupation using JMP 13.0 software (SAS Institute Inc., Cary, NC, USA). The significance of the mean ± SD values of the remaining survey results was analyzed by the paired *t*-test using Excel 2010 ver. 2010 software (Microsoft Corporation, Redmond, WA, USA). A p value $< 5\%$ was considered significant.

This study was approved by the Ethics Committee of the Showa University School of Medicine (Approval No. 1555).

Results

The study period was April 14 to May 14, 2014. A total of 40 subjects (14 men, 26 women) with a mean age of 36.6 ± 8.2 years (range: 26 to 55 years) who gave informed consent to participate in the survey during the study period were enrolled. The breakdown of subject occupations was as follows: 9 physicians, 10 nurses, 16 pharmacists, and 5 CRCs/administrative personnel.

There were no participants from outside the hospital, and no subject who had previously experienced using a B tablet or an S tablet was included (Table 2).

1. Disintegration time

The median values of the disintegration time for one tablet were 855.5 seconds/36.0 seconds (B tablet/S tablet). The disintegration times for one tablet classified by occupation were: physicians 706.0 seconds/38.0 seconds, nurses 786.0 seconds/32.0 seconds, pharmacists 987.0 seconds/34.0

Table 2. Subject demographics (n = 40)

	n (%)
Age (y)	36.6 ± 8.2
Male/Female	14/26 (35/65)
Physicians/nurses/pharmacists/CRCs & administrative personnel	9/10/16/5 (22.5/25/40/12.5)

CRCs, clinical research coordinators

seconds, and CRC/administrative personnel 1141.0 seconds/34.0 seconds (Figures 1, 2).

There was no significant difference in the tablet disintegration times by occupation.

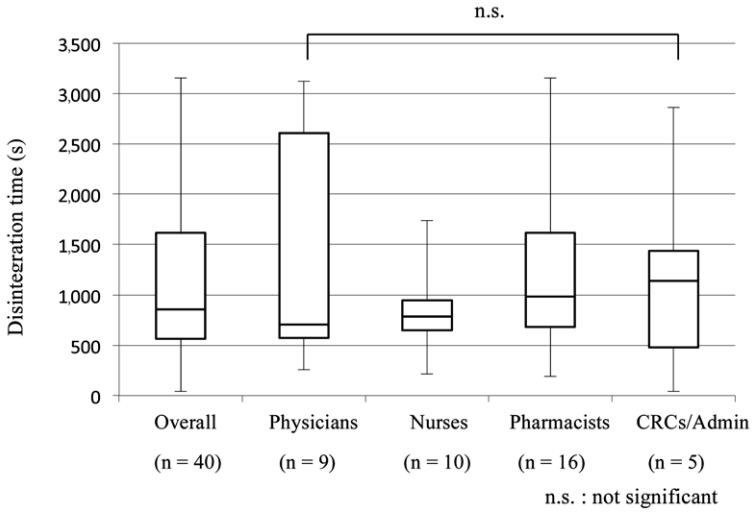

Fig. 1. Disintegration time of placebo buccal tablet

Box-plot graph of disintegration time shows the median values as lines across the box. Upper whiskers show maximum values, and lower whiskers show minimum values. The median value of the disintegration time for one tablet is 855.5 seconds overall (n = 40). The breakdown by occupation is as follows: physicians 706.0 seconds (n = 9); nurses 786.0 seconds (n = 10); pharmacists 987.0 seconds (n = 16); and CRCs / administrative personnel 1141.0 seconds (n = 5). (Kruskal-Wallis test). CRCs, clinical research coordinators; Admin, administrative personnel.

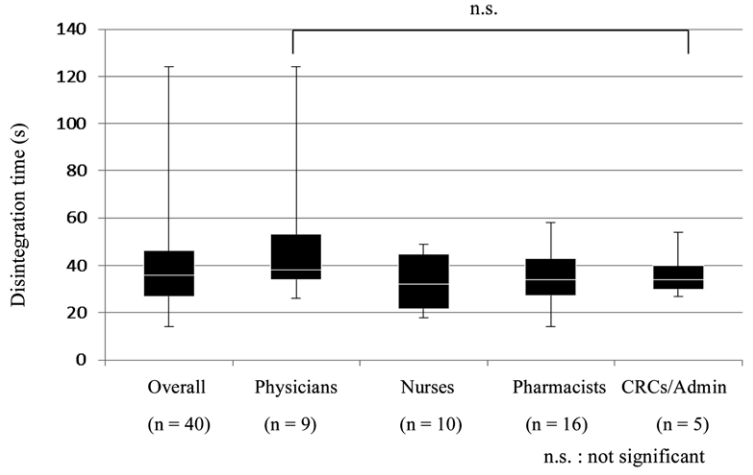

Fig. 2. Disintegration time of placebo sublingual tablet

Box-plot graph of disintegration time shows the median values as lines across the box. Upper whiskers shows maximum values, and lower whiskers shows minimum values. The median value of the disintegration time for one tablet is 36.0 seconds overall (n = 40). The breakdown by occupation is as follows: physicians 38.0 seconds (n = 9); nurses 32.0 seconds (n = 10); pharmacists 34.0 seconds (n = 16); and CRCs / administrative personnel 34.0 seconds (n = 5). (Kruskal-Wallis test).CRCs, clinical research coordinators; Admin, administrative personnel.

Table 3. Survey results : Median rating for user impression

	B tablet	S tablet	*P* value
Size	1.9 ± 1.0	1.6 ± 1.0	0.037
Ease of opening the sheet (package) and removing the tablet	1.5 ± 0.9	2.6 ± 1.1	< 0.001
Ease of holding	2.1 ± 1.0	2.0 ± 0.9	0.472
Ease of use (yourself)	1.6 ± 1.0	3.5 ± 1.1	< 0.001
Ease of use of tablet by another person	1.4 ± 0.8	3.5 ± 1.0	< 0.001
Palatability (flavor, effervescence)	1.6 ± 1.0	3.7 ± 1.0	< 0.001
Overall impression of tablet use (patient)	1.7 ± 1.0	3.6 ± 0.8	< 0.001
Overall impression of tablet use (another person)	1.5 ± 0.9	3.4 ± 1.0	< 0.001

B tablet : placebo buccal tablet, S tablet : placebo sublingual tablet
n = 40 Paired *t*-test : $P < 0.05$
Evaluation on a 6-step Likert-type scale with 5 representing extremely positive and 0 representing extremely negative. The scores were tallied, and the mean ± SD values were compared between the B tablet and the S tablet.

2. Survey results

The mean ± SD values of the results of the survey were as follows (B tablet/S tablet) : tablet size 1.9 ± 1.0 points/1.6 ± 1.0 points ; ease of opening the sheet (package) and removing the tablet 1.5 ± 0.9 points/2.6 ± 1.1 points ; ease of holding the tablet 2.1 ± 1.0 points/2.0 ± 0.9 points ; ease of use of the tablet oneself 1.6 ± 1.0 points/3.5 ± 1.1 points ; ease of use of tablet by another person 1.4 ± 0.8 points/3.5 ± 1.0 points ; impression associated with flavor and effervescence (palatability) 1.6 ± 1.0 points/3.7 ± 1.0 points ; overall impression of use of the tablet by the patient 1.7 ± 1.0 points/3.6 ± 0.8 points ; and overall impression of use of tablet by another person 1.5 ± 0.9 points/3.4 ± 1.0 points.

The results of the statistical analysis showed significant differences between the B tablet and the S tablet in all items except ease of holding the tablet (Table 3).

For "Other (free-text comments)", 31 persons entered their impressions after use, with the B tablet given descriptions of "unpleasant" and "irritating". While there were opinions about the S tablet such as "convenient" and "good flavor", there were also subjects who felt "anxiety" because the tablet "moved around under my tongue" and "dissolved very quickly" (Table 4).

Discussion

Among the subjects in this study, the S tablet disintegrated in the mouth in about one minute, while the B tablet took approximately 14 minutes. Previous studies have reported disintegration times of less than 2 minutes for the sublingual tablet[7], and 14 to 25 minutes for the buccal tablet[8], which are essentially the same as in this study, although the disintegration time tended to be shorter in our hospital. Various factors can affect the disintegration of tablets, such as formulation type, human factors, and the oral environment, and there might be differences among study settings in understanding the location of use of the tablet or in explanations of tablet use.

In the summary of product characteristics of each formulation, the maximum concentration

Table 4. Survey results : Other (free-text comments)

[Physicians]		
Handling method, usage method, location	B tablet	• The package is difficult to open. • The tablet was too small and drifted toward the back molars. • The mucosa had an uncomfortable swollen feeling, and if this happens every time it will be difficult for the patient to use.
	Both	• The tablets were small and will be difficult for an elderly person to handle. • Sticking a finger into the mouth to find the tablet was unpleasant.
Flavor	B tablet	• The salty flavor and foaming bothered me, and I wanted the tablet to dissolve quickly.
[Nurses]		
Handling method, usage method, location	B tablet	• The package was too stiff, and I almost dropped the tablet.
	S tablet	• The tablet moved around in my mouth, and it was difficult to use.
Flavor	B tablet	• The flavor stuck in my throat and coated it. • The flavor lingered for a while after the tablet had dissolved completely, and that was unpleasant. • The first stimulus was tartness.
	S tablet	• The flavor was not an issue, and my impression was that the tablet was convenient.
[Pharmacists]		
Handling method, usage method, location	B tablet	• Because the tablet was so small, I could not feel it in my mouth. • My gum started to hurt. • It was difficult to know if I was able to use the tablet correctly. • I felt that I could relax and use the product confidently. • It irritated my teeth and was difficult to use. • I was worried it might fall out if I laughed. • I could not tell if it was still there.
	S tablet	• It would be easier to administer if it was a little larger. It is easy to use with a mirror. • I had trouble keeping it fixed under my tongue without swallowing it. • Because it dissolved quickly, there was no stress. • I had the impression that it started to dissolve before I placed it under my tongue, and felt anxious about whether it contained a large enough dose to be absorbed from under my tongue. • It was easy to remove the tablet, and the flavor was good, but there is a good chance that a child could ingest it by mistake. Instructions about proper control are important.
	Both	• I was worried whether it could be used as instructed.
Flavor	B tablet	• The flavor was not unpleasant, but I would not want to use it when I don't feel good. • It irritates the tongue and has a metallic flavor. I felt as if my mucosa were swelling. • It felt uncomfortable where I placed it and was irritating when it touched my tongue. That was unpleasant.
Disintegration time	B tablet	• It took a long time to dissolve, and I was anxious about whether it would be effective.
	S tablet	• The tablet dissolved quickly, and that was convenient.
[CRCs & Administrative personnel]		
Flavor	B tablet	• It tingled and felt irritating.

(Selected excerpts)

B tablet : placebo buccal tablet, S tablet : placebo sublingual tablet
CRCs, clinical research coordinators

time (T_{max}) for a single dose of the buccal tablet was 0.585[9] hours (two 50 μg tablets positioned buccally and the remainder swallowed after 30 minutes), and the T_{max} for the sublingual tablet was essentially the same at 0.50 hours (100 μg administered sublingually). To obtain a higher

blood concentration "OraVescent® technology" is used in the buccal tablet to impart carbon dioxide effervescence and pH regulation, and higher bioavailability can be obtained through more rapid absorption via the oral mucosa[9]. Likewise, the sublingual tablet is manufactured by compounding the fentanyl citrate (bulk), a disintegrant, and a mucoadhesive agent into carrier particles; the tablet is designed to be retained at the administration site, and the fentanyl is absorbed via the oral mucosa[10]. Because of the designs of the formulations, the bioavailability exhibits essentially similar pharmacokinetic parameters that are independent of the disintegration time, with 65% for the buccal tablet and 50% for the sublingual tablet, although if an ROO formulation is not used properly, the expected usefulness cannot be attained. Based on the present study, we can inform the patient about disintegration time and the product characteristics before using the medicine. The patient can then continue to use the formulation without anxiety.

In the evaluations of tablet size and ease of holding, the larger B tablet scored better. In a previous study of elderly patients, the one closer to 7 mm is the easiest to hold[11]. In this study group, the S tablet packaged in a strip package (SP) sheet scored more favorably in ease of opening the package and removing the tablet than the B tablet packaged in a blister pack. The B tablet blister pack is a childproof sheet, designed to prevent accidental ingestion; however, even adults sometimes struggle to open the package, and opening the package requires an explanation (Figures 3-A, B).

Regarding flavor, many subjects stated that the acidity, saltiness, and effervescence of the B tablet were unpleasant, whereas some subjects thought the S tablet had a subtle sweetness. The B tablet contains a foaming agent and pH regulators (anhydrous citric acid, sodium bicarbonate, dried sodium carbonate), and the S tablet contains D-mannitol as factors that contribute to the flavor. Overall, in the present study, the subjects truly sensed differences in flavor and effervescence; however, in the real clinical situation, only one formulation will be selected by a patient, so the patient cannot compare the formulations. It is therefore important for the medical staff to describe factors such as flavor and sensation to the patient during the use of a formulation. With the B tablet, the "buccal" site of administration must also be explained, and based on this survey, we predict that there will be problems with drug administration, such as the patient's misunderstanding of the location.

With both the B tablet and the S tablet, it is difficult to know when the product has

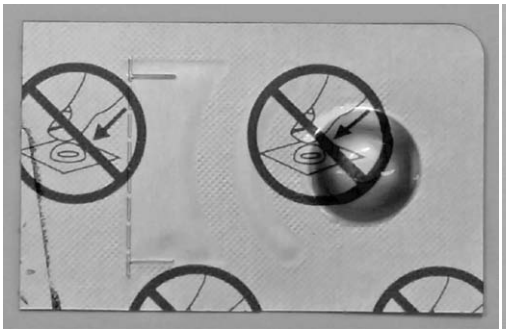

Fig. 3-A. Blister pack

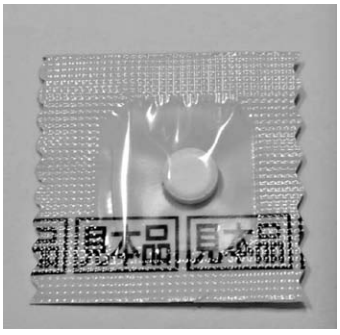

Fig. 3-B. Strip package

completely dissolved. During the dose titration period, the patient may experience a period of anxiety until the medication starts to take effect, particularly with ROO formulations. Medical staff must devise creative solutions for such matters including how to explain in concrete terms the disintegration time and the estimated time for the drug to take effect before the patient begins using the product. The survey results of the present study have shown better ways to explain such features of the medication beforehand so as to reduce patient anxiety.

This study was expected to enable accumulation of the key points for actual use by patients across multiple occupations, but no major differences in the content of the comments were found. However, physicians and nurses mainly commented on flavor and impressions after use, and many pharmacists commented on handling methods in addition to user impressions such as flavor and irritation. This result reflects the various work roles of the included occupations to an extent. User impressions were common across all occupations, and they are predicted to be similar to those of actual patients. The B tablet was considered "difficult to handle", and the S tablet was "convenient", but both tablets elicited strong "anxiety" about their use. When educating the patient, medical staff must strive to mitigate patient anxiety by providing information not only on the usage method, location of use, points to remember during administration, and method of storage, but also on disintegration time, estimated time for the drug to take effect, and the flavor and sensations during use.

This study used a placebo to compare the ease of use and sensations during use of TIRF buccal and sublingual tablets with different routes of administration, and it found that the sublingual tablet was easier to use and the sensations during use were more favorable compared to the buccal mode. Moreover, because scattering was found in the disintegration time even when a similar explanation was given, it is possible that efficacy will differ depending on the method of explanation and the patient's understanding. Therefore, the sublingual tablet, which had less scattering in the present study, will be more useful clinically.

Fentanyl citrate is a drug with low bioavailability when used orally, but if sufficient efficacy can be obtained through buccal and sublingual routes, it will be useful for improving the quality of life of patients who have struggled with pain control in the past, especially cancer pain patients who have difficulty swallowing and taking oral medications, and patients with inadequate pain control due to adverse reactions to morphine hydrochloride and oxycodone hydrochloride.

The subjects in this study were relatively young adults, and it has been pointed out that many actual patients would be elderly[12, 13]. Moreover, because these products are likely to be used for cancer pain, observation focusing on the patient's condition will be necessary when the products are used with patients who have a compromised oral environment because of oral tumors or adverse reactions in the oral cavity from chemotherapy with anticancer drugs and radiation therapy (such as stomatitis, oral hemorrhage, oral mucosa deficiency, oral candidiasis, osteonecrosis of the jaw, and dry mouth).

In the present study, the median values of the disintegration time for one tablet were similar to those in previous reports, but in fact the individual difference was large. In addition, based on the participants' impressions, it was found that because of the dosage form with less experience

of use, the handling method seems difficult, causing unease. In this study, important information about the two tablet formulations, such as disintegration time, tablet size, and ease of opening the sheet (package) and removing the tablet, was collected for patient education. Furthermore, as information necessary for proper use, we will explain the standard time when drugs will be effective, attention to handling, flavor and others, so that the patient does not feel anxious.

Patient education by medical staff will help to promote proper use of medicine by using product characteristics and user impressions obtained in this study. In addition, the time and feeling of the effect of fentanyl citrate sublingual tablets will be investigated in actual patients in the future.

Conflict of interest disclosure

The authors of this paper have no conflict of interest to disclose.

References

1) World Health Organization. Cancer pain relief: with a guide to opioid availability. 2nd ed. Geneva: World Health Organization; 1996.
2) Guitart J, Vargas I, De Sanctis V, *et al*. Efficacy and safety of sublingual fentanyl orally disintegrating tablets in patients with breakthrough pain: multicentre prospective study. *Clin Drug Investig*. 2013;**33**:675−683.
3) Zeppetella G, Davies A, Eijgelshoven I, *et al*. A network meta-analysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes. *J Pain Symptom Manage*. 2014;**47**:772−785. e5.
4) England R, Maddocks M, Manderson C, *et al*. How practical are transmucosal fentanyl products for breakthrough cancer pain? Novel use of placebo formulations to survey user opinion. *BMJ Support Palliat Care*. 2011;**1**:349−351.
5) Uberall MA, Muller-Schwefe GH. Sublingual fentanyl orally disintegrating tablet in daily practice: efficacy, safety and tolerability in patients with breakthrough cancer pain. *Curr Med Res Opin*. 2011;**27**:1385−1394.
6) Nakamura C, Toyama Y, Hisada T, *et al*. Comporative study on the usability of E-fen buccal tablet and abstral sublingual tablet by using those preparation exanples. *J Jpn Soc Hosp Pharm*. 2016;**52**:877−881. (in Japanese).
7) Nalamachu S. Anevaluation of total disintegration time for three different doses of sublingual fentanyl tablets in patients with breakthrough pain. *Pain Ther*. 2013;**2**:121−128.
8) Darwish M, Kirby M, Jiang JG. Effect of buccal dwell time on the pharmacokinetic profile of fentanyl buccal tablet. *Expert Opin Pharmacother*. 2007;**8**:2011−2016.
9) Interview form of "E-fen(R) buccal tablet 50 μg・100 μg・200 μg・400 μg・600 μg・800 μg". (Revised July 2016) (accessed 2016 Oct 5) Available from: https://www.taiho.co.jp/medical/brand/e-fen/pdf/78G001G.pdf
10) Interview form of "Abstral Sublingual Tablet". (Revised May 2016) (accessed 2016 Oct 05) Available from: http://www.kksmile.com/druginfo/yakuzai_pain/interv/abs_in.pdf
11) Hashimoto T. Survey on medication compliance and awareness of dosage form in elderly patients. *Ther Res*. 2006;**27**:1219−1225. (in Japanese).
12) Okida M, Okada K, Sanuki M, *et al*. Experience of the management of cancer pain in 119 patients who were treated during 1999～2001 in Japan. *Symptom Manage Cancer Patients*. 2003;**14**:80−85. (in Japanese).
13) Ministry of Health, Labour and Welfare. The results of the 2014 patient survey (Internet). 2015. (in Japanese). (accessed 2016 Oct 5) Available from: http://www.mhlw.go.jp/toukei/saikin/hw/kanja/14/dl/toukei.pdf

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