



Original experimental

Facilitation of accurate and effective radiation therapy using fentanyl pectin nasal spray (FPNS) to reduce incidental breakthrough pain due to procedure positioning



Isabel Prieto^{a,*}, José Pardo^b, Javier Luna^a, Juan P. Marin^a, Jesús Olivera^a, Antonio J. Garcia^c, Ana M. Perez^a

^a Radiation Oncology Department, Fundación Jiménez Díaz University Hospital, Madrid, Spain

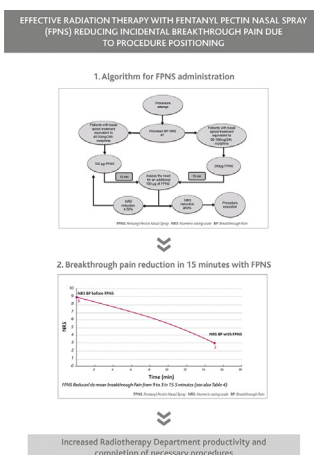
^b Radiation Oncology Department, Son Espases University Hospital, Palma de Mallorca, Spain

^c Cátedra de Economía de la Salud y Uso Racional del Medicamento, Pharmacology Department, University of Medicine, Málaga, Spain

HIGHLIGHTS

- Poor pain control in radiotherapy results in diminished quality of treatment.
- This work describes a precise protocol to ensure adequate oncological pain control.
- Using fentanyl pectin nasal spray may help to decrease oncological pain rapidly.
- This pain control improves the workflow in the Radiation Oncology Department.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:

Received 4 November 2015

Received in revised form 1 December 2015

Accepted 3 December 2015

Available online 29 December 2015

Keywords:

Radiotherapy

Procedure

Pain

Fentanyl

Intranasal

Visual analogue scale

ABSTRACT

Purpose: To provide effective and accurate radiotherapy (RT) for advanced cancer patients who experience breakthrough pain (BP) due to positioning manoeuvres, through the use of FPNS. Secondary endpoints were the dose and time required to achieve a 50% numeric rating scale (NRS) reduction and conduction of a pharmacoeconomic analysis.

Patients and methods: Twenty-seven advanced cancer patients with moderate-severe BP associated with routine radiotherapy procedures and manoeuvres were selected to receive FPNS. Most patients (20/27) had bone metastases. The patients showed a low Karnovsky performance status (mean 54%; range: 30–80). BP intensity was scored with the NRS before and after the procedures that triggered it. All patients were already receiving opioid baseline treatment at a total dose equivalent to 40–160 mg oral morphine. Before the procedure, BP was treated with 100–400 µg of FPNS. Data related to tolerance, pain relief, onset of the relief and efficient dose to allow RT to proceed were collected.

Results: In 26 patients the BP score was reduced by at least 50% as determined in 15 min (range 8–35 min) after fentanyl pectin intranasal administration, and pain relief started after 7 min

DOI of refers to article: <http://dx.doi.org/10.1016/j.sjpain.2015.12.008>.

* Corresponding author. Tel.: +34 656956571.

E-mail addresses: iprieto@fjd.es (I. Prieto), jose.pardo@ssib.es (J. Pardo), jluna@fjd.es (J. Luna), jolivera@fjd.es (J. Olivera), amperez@fjd.es (A.M. Perez).

<http://dx.doi.org/10.1016/j.sjpain.2015.12.001>

1877-8860/© 2015 Scandinavian Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

(range 3–15 min); $p < 0.05$ in both cases. The duration of pain reduction facilitated the proceeding of RT. The Mean NRS score before the procedure was 9 (95%CI: 8.6–9.4) and decreased during procedure to 3 (95%CI: 2.5–3.8). The average dose of FPNS for most patients was 100–200 μg to achieve pain control, except in three patients who required progressive doses of up to 300–400 μg . After receiving 300 μg , one patient dropped out of the study due to severe adverse effects (nausea). Seven patients reported minor undesirable effects related to FPNS administration.

Conclusions and implications: Certain necessary RT procedures in advanced cancer patients can cause severe BP episodes. A simple, safe, fast acting and strong analgesic is needed. FPNS is a rapidly absorbed opioid analgesic with a pain relief profile that would be particularly well suited for this patient population. By reducing BP, the drug enables the completion of necessary RT procedures without needless patient discomfort. When BP is attenuated, Department productivity is maintained and unnecessary delays are avoided. Further studies and clinical trials are needed to assess therapeutic FPNS dosages with a view to defining efficacy in the correct clinical context.

© 2015 Scandinavian Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

1. Introduction

Radiation therapy (RT) procedures are performed in different steps that should be carefully and efficiently executed according to a specific framework [1]. During the design and delivery of treatment, with linear accelerators or brachytherapy techniques, patients must remain motionless on an uncomfortable X-ray table while required to hold positions that cause pain. In advanced cancer patients, these manoeuvres frequently trigger breakthrough pain (BP) episodes that complicate completion of all the steps. Effective management of such breakthrough pain has been shown to be difficult, and constitutes a frequent problem for both the physician and patient. Unfortunately, general anaesthesia cannot be used in our procedures, since patient collaboration is needed. Furthermore, anaesthesia would add risks and important personnel and material costs. Suitable pain relief should be effective, quick, tolerable and easy to administer, with the patient awake and collaborating. Patients experiencing pain will delay completion of the procedure, and RT might not be accurately administered. This delay interferes with the workflow of the Department and increases clinical expenditures.

Breakthrough pain, as defined by Portenoy et al. in 2004 [2], is a transient exacerbation of pain experienced by a patient who has relatively stable and adequately controlled baseline pain. Episodes of breakthrough pain typically occur frequently, are of moderate to severe intensity, and have a rapid onset (minutes) and a short duration [3–5].

Prior to this study, we reviewed the published literature regarding painful procedures in cancer patients, looking for solutions for this problem. The literature search revealed a lack of satisfactory information. Oral transmucosal fentanyl citrate is the most frequently used preparation for breakthrough pain in Spanish hospitals and Oncology Departments [6]. However, based on our experience, patients treated with oral transmucosal fentanyl citrate show poor results in terms of the prevention of breakthrough pain during procedures in radiotherapy. Some publications suggest the superiority of a new-generation fentanyl, in contrast to the most widely used standard treatment for breakthrough pain [7–11]. Published data demonstrate that the pharmacokinetic features of nasal fentanyl pectin administered under crisis conditions afford better results in terms of breakthrough pain control than transmucosal formulations [12,13]. Blanco et al. [13] examined the efficacy of fentanyl pectin nasal spray (FPNS) versus other transmucosal fentanyl formulations, and introduced the term years gained with good quality of life. This term defines the numbers of years gained with good quality of life after controlling breakthrough pain. The authors

found that more quality-adjusted life years were gained for patients treated with FPNS. A decrease in associated costs was also observed with FPNS versus other fentanyl applications. Other authors have published studies on the efficacy and tolerance of other opioids in controlling breakthrough pain in cancer patients, with rapid effects and low toxicity [14,15]. Taylor et al. [16] investigated 163 patients with recurrent breakthrough pain treated with FPNS, reporting adequate pain control and fair tolerance. Fallon et al. [7] in turn demonstrated superior and earlier effectiveness with FPNS versus immediate-release oral morphine sulfate in the treatment of breakthrough cancer pain. Zeppetella et al. [14] recently published a metaanalysis of the impact of opioid analgesics in the management of breakthrough cancer pain episodes. A systematic literature search (2007–2010) yielded 10 randomized controlled trials that investigated the effects of breakthrough cancer pain medications. The analysis included intranasal/transmucosal fentanyl and immediate-release morphine sulfate. The study concluded that although all the analyzed medications provided pain relief, transmucosal fentanyl achieved a greater level of pain relief in a shorter time than either placebo or oral morphine. The authors added that intranasal fentanyl provided the greatest improvement. Very recently, Bell and Butler have published five cases of predictable pain in patients undergoing radiotherapy. FPNS offered a good solution for the control of breakthrough pain episodes, and minimized interruptions in the radiotherapy schedule [17].

On examining the summaries of product characteristics of the main transmucosal fentanyl formulations, it is seen that FPNS offers a number of advantages: immediate administration, faster onset of action, lesser time to maximum concentration (T_{max}), no need for saliva, and greater bioavailability (Table 1) [18–22]. In comparison, nasal fentanyl in water can result in nasal or postnasal dripping, and this leads to important analgesic variability between episodes. We therefore do not consider it to be an adequate choice.

Based on the above evidence, FPNS could be considered good option for relieving breakthrough pain caused by radiotherapy procedures, and for allowing the completion of procedures. For this reason, we decided to conduct a prospective study with fentanyl pectin nasal spray. The first clinical endpoint was to assess the breakthrough pain relief obtained with FPNS in cancer patients describing moderate to intense pain during the crucial procedures in radiotherapy. Secondary endpoints were the titration dose needed to prevent/relieve breakthrough pain (dose and time required to achieve a 50% reduction on the numeric rating scale - NRS-), and the conduction of a simple cost utility analysis. We also analyzed the start of action of FPNS and its toxicity profile, and documented treatment compliance.

Table 1
Comparison of the different forms of application of transmucosal fentanyl [18–22].

FENTANYL	Actiq®	Effentora®	Abstral®	Pecfent®
Administration	Oral transmucosal applicator	Oral transmucosal tablet	Sublingual tablet	Fentanyl pectin nasal spray
Application time (min)	15'	14' to 25'	Rapid dissolution	Immediate application
Onset of analgesia (min)	15'	10' to 15'	10'	5'
Time to maximum concentration, T_{max} (min)	20' to 40'	46.8'	22.5' to 240'	15' to 21'
Starting dose (μg)	200	100	100	100
Self-adjustable	Yes	No	No	No
Need for titration	Yes	Yes	Yes	Yes
Need for saliva	Yes	Yes	Yes	No
Possible local toxicity	Yes	Yes	Yes	Yes
Bioavailability	50%	65%	70%	70–90%

2. Methods and materials

From September 2013 through October 2014, a total of 27 patients with advanced cancer and moderate to severe breakthrough pain associated with routine radiotherapy procedures received FPNS for pain relief. The study was designed as a point intervention to alleviate breakthrough pain associated with positioning or manoeuvres during radiotherapy procedures. Patients were treated at the Fundación Jimenez Diaz and Son Espases University Hospital Radiation Oncology Departments (Spain). FPNS is approved for moderate to severe breakthrough pain. However, keeping in mind the aetiology of this type of pain, the survey was approved by the Ethic Committees. Written informed consent was obtained from all patients according to the guidelines for Good Clinical Practice.

A numeric rating scale (NRS) was used to evaluate breakthrough pain intensity and treatment efficacy. On starting the procedure pain intensity was monitored by asking the patient to verbally score pain from 0 to 10, where 0 = no pain and 10 = unbearable pain. This verbal evaluation was made repeatedly by the medical and nursing personnel during the observational process with each patient – especially if some change in gesture or anti-pain posture was noted. Likewise, the patients were asked to report all analgesic responses from administration of the drug, along with the changes in pain intensity (relief or worsening). Such close patient monitoring allowed identification of the time of onset of relief and the real-time evolution of pain before and after administration of the drug. Other tools for assessing pain impact, satisfaction or wellness were not considered.

Inclusion criteria:

Patients suffering from any type of cancer pain for which radiotherapy is prescribed.

Patients describing moderate to severe breakthrough pain related with positioning or procedures, with a NRS score of ≥ 7 (NRS 7–10) and already receiving baseline opioid treatment at a total dose equivalent to 40–160 mg/day of oral morphine.

The algorithm shown in Fig. 1 was followed for FPNS administration. Breakthrough pain intensity was evaluated with the patient from the start of the observational process, and especially at three timepoints: before the radiotherapy procedure or manoeuvres that triggered the pain, in the 5–10 min after FPNS administration, and while the procedure was being carried out. The aim was to achieve sufficient pain relief to allow the patient to be comfortable during the procedure. Pain relief was considered adequate when the NRS score was decreased by at least 50%.

Patients with baseline opioid treatment at a dose equivalent to 40–50 mg/day of oral morphine received one initial intranasal titration dose of 100 μg of FPNS. An initial intranasal titration dose of 200 μg of FPNS was administered to patients with baseline opioid treatment at a dose equivalent to 60–160 mg/day.

In those cases where the effect 15 min after first intranasal fentanyl administration was insufficient to decrease the breakthrough pain score by at least 50%, we administered a second dose of 100 μg of FPNS in the contralateral nostril. Additional NRS evaluations were made every 15 min after the second and consecutive FPNS administrations until the pursued pain relief was achieved or intense adverse effects appeared. The maximum administered FPNS dose in this study was 400 μg .

Patients were asked to report any undesirable symptoms related to fentanyl administration. Data related to tolerance, pain relief duration, onset of relief, and efficient dose allowing completion of the procedure were collected. A pharmacoeconomic (cost-effectiveness/utility) analysis was also carried out.

Regarding costs, we only considered those related to the medication prescribed for breakthrough pain relief during the radiotherapy procedure (test-session-technique).

The calculation of utilities was based on an analysis of the difference in pain reduction (as assessed by the NRS score) before versus after administration of the medication for controlling breakthrough pain during the radiotherapy procedure. Utility represents the gain in good quality of life of the patient and is expressed as the quality-adjusted life years gained (QALYs) – the latter being calculated from a mathematical (generalized least squares (GLS)) model using the following formula [23]:

$$\text{Utility (pain)} = (\beta * NRS_{\text{pain final}} + \beta^2 * NRS_{\text{pain final}}^2) - (\beta * NRS_{\text{pain initial}} + \beta^2 * NRS_{\text{pain initial}}^2)$$

where: $\beta = -0.00120$; $\beta^2 = -0.0000069$.

Oddershede et al. developed a model to predict the utility score from 5 NRS scores in which patients rate mobility, self-care, ability to perform usual activities, pain, and anxiety and depression, based on the EQ-5D [23]. We applied the model to map the partial effect of reducing patient pain measured on a NRS to utility scores, under the ceteris paribus assumption, i.e., keeping all other factors fixed.

In addition to pain reduction assessed by the NRS score, the calculation of effectiveness (efficacy of treatment in our patients) considered the time (minutes) to the onset of pain relief, and the time and dose required to reach a 50% decrease in the NRS pain-intensity score [24].

The descriptive statistical study involved calculation of the mean, standard deviation (SD) and 95% confidence interval (95%CI) for quantitative variables, and frequencies and proportions in the

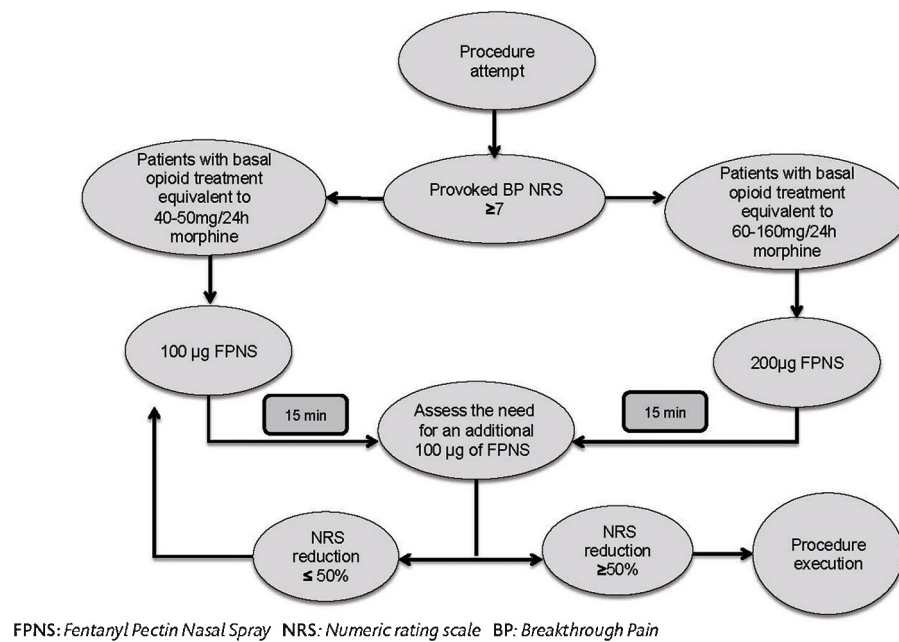


Fig. 1. Algorithm FPNS.

Table 2
Diagnose.

Diagnose	N	% Patients
Myeloma	3	11.1%
Cervical mts/unknown	2	7.4%
Bone/lymphoma	1	3.7%
Brain mts	1	3.7%
Bone mts/lung	9	33.3%
Bone mts/prostate	3	11.1%
Bone mts/breast	3	11.1%
Bone mts/thyroid	1	3.7%
Bone mts/oropharynx	1	3.7%
Bone mts/urologic	1	3.7%
Bone mts/colon	1	3.7%
Bone mts/unknown	1	3.7%
Total	27	100.0%

case of qualitative variables. Comparison of variables in turn was based on the Wilcoxon nonparametric test for quantitative variables and the chi-squared test for qualitative variables.

3. Results

Cancer pain and reported moderate to severe breakthrough pain, with a score of ≥ 7 (NRS range 7–10), most often located in the same site targeted for irradiation. All patients showed a low Karnofsky performance status (mean 54%; range: 30–80). Ten of the patients were females (37.0%). The average age was 68.5 years (range 52–87). Three patients suffered bone pain due to myeloma; two had a painful neck mass secondary to lymphatic metastases; one described bone pain due to lymphoma; one had headache secondary to brain metastases; and 20 suffered bone pain due to metastatic disease secondary to different primary tumours (tumours of the lung, prostate, breast, thyroid, oropharynx, urological tract, colon, and unknown) (Table 2).

All patients were already receiving baseline opioid treatment at a total dose equivalent to 40–160 mg/day of morphine (mean: 80 mg; 95%CI: 61–99). Breakthrough pain occurred at the attempted radiotherapy procedure. The procedure consisted of a treatment design (positioning/immobilization) followed by computed tomography imaging or treatment delivery (Table 3). Due to

Table 3
Radiotherapy procedures.

Radiotherapy procedures	N	% Patients
CTIA	14	51.9%
TD	8	29.6%
CTIA + TD	5	18.5%
Total	27	100.0%

CTIA, computed tomography image acquisition.
TD, treatment delivery.

the intensity of the pain, all procedures were interrupted and FPNS treatment was administered to relieve the pain. Table 4 shows the patient and pain data.

The procedures that most frequently caused breakthrough pain in the group of 27 patients were positioning/immobilization for treatment design and computed tomography imaging. The mechanism triggering such breakthrough pain was always related to the manoeuvres required for motionless positioning. The location of the breakthrough pain area coincided with the targeted area for irradiation in 24 patients. In all cases, breakthrough pain had somatic and mixed features, with variable intensity.

In all patients, the mean baseline pain score was 6 (NRS range 2–10), and the mean breakthrough pain score at attempted radiotherapy procedure was 9 (NRS range 7–10). The mean score was reduced by 6 points after FPNS administration. All but four patients reported control of breakthrough pain with an initial dose of 100 or 200 µg of FPNS. Three patients required doses up to 300 and 400 µg to relieve the pain. These patients who required more doses were receiving an equivalent daily oral morphine dose of 40, 100, and 160 mg, respectively, for baseline pain. The fourth patient did not achieve relief, and FPNS administration was interrupted after 300 µg due to intense adverse events (dizziness and nausea) described in the FPNS fact sheet. For the rest of 23 patients, the mean breakthrough pain score during the radiotherapy procedures and after FPNS administration was 3 (NRS range 0–5).

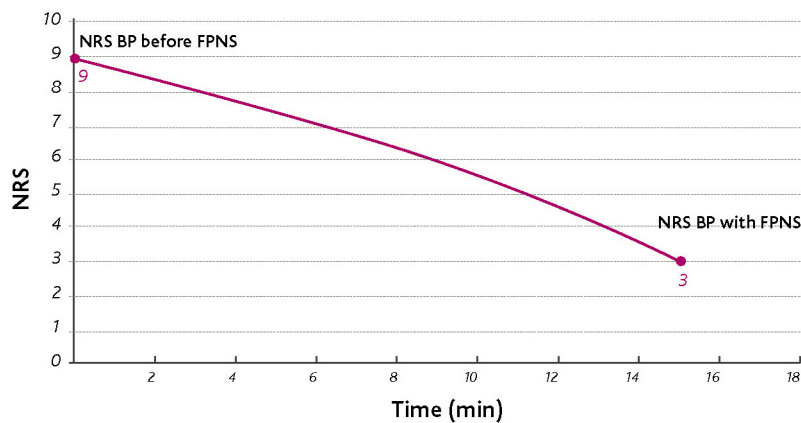
The mean time needed to achieve a decrease in breakthrough pain of at least 50% was 15.5 min (range 8–35 min). Pain relief began after 7 min (range 3–15 min), and the duration of the effect allowed the normal procedure to be carried out in the treated patients

Table 4
Patient's characteristics and pain data. N = 27.

Patient's characteristics			
Variable	Mean	SD	Range
Age (years)	68.5	11.6	52–87
Karnovsky performance status	54	16	30–80
<i>Pain data</i>			
Morphine doses for basal pain	80 mg	47.9 mg	40–160 mg
FPNS doses for breakthrough pain	169 µg	78.8 µg	100–400 µg
NRS breakthrough pain ^a	Before procedure	9	7–10
	During procedure (after FPNS administration)	3.2	0–5
Absolute difference in pain intensity [24] (PID: 0–10 scale)	6	1.3	4–9
Effectiveness–percentage difference in pain intensity [24] (PID%: 0–100 scale)	65.0%	16.4%	50–100%
FPNS start of action	7 min	2.8 min	3–15 min
FPNS time to 50% NRS reduction	15.5 min	6.8 min	8–35 min

^a Nonparametric test: Wilcoxon; *p* value < 0.001.

FPNS, fentanyl pectin nasal spray.



FPNS Reduced de mean breakthrough Pain from 9 to 3 in 15.5 minutes (see also Table 4)

FPNS: Fentanyl Pectin Nasal Spray NRS: Numeric rating scale BP: Breakthrough Pain

Fig. 2. BTPc Reduction with FPNS.

(Table 4 and Fig. 2). The adequacy in time of FPNS analgesia applied to radiation oncology procedures is warranted by the duration of the procedures (about 25–30 min) and the fact that the pivotal FPNS study demonstrated gradual improvement of analgesia versus the comparator drug, from 5 to 60 min [25].

The patients included in this study repeated FPNS administration in consecutive procedures when it was needed, with the same successful results.

The time to action of FPNS was less than 5 min in almost 50% of the patients. For almost 70% of the patients the time needed to achieve a 50% decrease in NRS score was less than 15 min (Fig. 3).

No statistically significant differences (Mann–Whitney *U*-test) were observed regarding the variables sex and effectiveness, morphine doses, FPNS doses required, rescue doses, relief onset and time to 50% NRS reduction. In contrast, statistical significance (*p* < 0.05) was recorded in relation to the difference in NRS score (NRS before procedure – NRS during procedure) likewise referred to the above variables and the type of radiotherapy procedure (Kruskal–Wallis test) or the Karnofsky performance status (Mann–Whitney *U*-test).

Seven patients reported minor undesirable effects related to the administration of FPNS (dizziness in 5 patients and drowsiness in 2 cases). One patient dropped out of the study due to severe dizziness and intense nausea. FPNS was well tolerated (>73% of patients), and no complications related to the intranasal administration were recorded.

Table 5
Cost utility analysis.

Variable	Mean	SD	CI 95%
Cost of medication	14.8 €	6.3 €	12–17 €
Effectiveness	62.6%	20%	55–71%
Cost-effectiveness analysis (CEA) ^a	23.6	11.5	18.8–28.1
Utility (QALY gained by decreasing pain) ^b	0.1113	0.0303	0.0994–0.1233
Cost-Utility Analysis (CUA) ^c	129.5 €	66.7 €	103–157 €

^a (Cost/effectiveness) × 100.

^b Utility (pain) = $(\beta * NRS_{final} + \beta^2 * NRS_{final}^2) - (\beta * NRS_{initial} + \beta^2 * NRS_{initial}^2)$ [$\beta = -0.00120$; $\beta^2 = -0.0000069$].

^c Cost of medication/utility.

3.1. Cost utility analysis

The results of the pharmacoeconomic analysis are shown in Table 5. Effectiveness was measured as pain reduction after FPNS for the radiotherapy procedure (as a percentage of the NRS score),

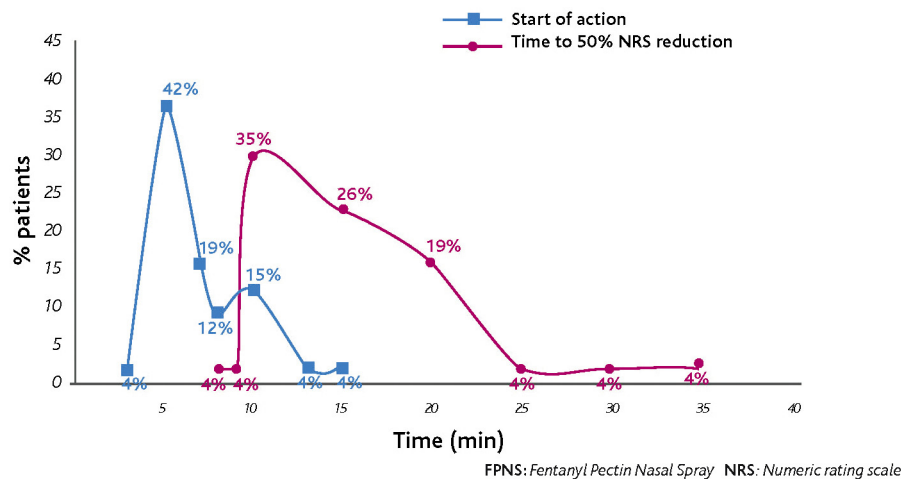


Fig. 3. FPNS Start of Action.

where 100% effectiveness corresponded to absolute pain reduction and 0% to no pain reduction.

The formula mentioned in the methods section yielded quality of life (utility or QALY) thanks to the decrease in breakthrough pain NRS score with FPNS.

The average cost per patient for pain control and conduction of the radiotherapy manoeuvres was just under 15€. This figure was calculated considering the price of FPNS in Spain and the mean FPNS doses required for breakthrough pain: 169 µg as shown in Table 4 (i.e., we found that most patients required 100–200 µg of FPNS to control breakthrough pain in routine radiotherapy procedures and manoeuvres).

We found that the costs of significantly improving the quality of life of patients or all the dimensions of the EuroQoL questionnaire (i.e., using the treatment for a longer period of time to improve mobility, self-care, ability to perform usual activities, pain, and anxiety and depression) would have been close to 130€ per patient (Table 5).

It should be noted that other expenses such as opportunity costs and the interruption of work flow also decrease with breakthrough pain relief thanks to FPNS. Radiation oncology procedures require the intervention of 1–3 technicians, a nurse and a physician. Furthermore, these professionals use technological equipment (linear accelerator or CT) that imply added costs (machine time). Procedures that cannot be successfully completed generate both opportunity costs (wasted personnel and machine time) and added real costs, since the procedure must be postponed for another day – with the associated new personnel and machine costs this implies. It is difficult to calculate the cost savings without the use of control groups. Nevertheless, it is clear that the costs would be far beyond the 15€ per patient required by FPNS, as demonstrated by our pharmacoeconomic analysis.

4. Discussion

Management of moderate to severe pain in cancer patients with disseminated disease. Palliative relief to the affected site is the conventional benefit of ionizing radiation treatments. However, radiotherapy procedures frequently cause breakthrough pain that prevent the entire procedure from being carried out.

Breakthrough pain is associated to a number of causes (e.g., the cancer itself, anticancer treatment, or concomitant illness), and physiopathological mechanisms (e.g., nociceptive, neuropathic or mixed). Effective management of breakthrough pain has proved difficult to achieve. Breakthrough pain in patients with advanced

cancer who are in need of radiotherapy can be related to positioning and treatment delivery. Furthermore, suitable relief should be effective, quick, tolerable, and easy to administer [26].

In our prospective study we included patients with incidental pain, which is understood to be a subtype of breakthrough pain induced by movement or some other voluntary action of the patient. In these cases voluntary actions are positioning and immobilizing actions. By controlling these predictable pain episodes as soon as possible, repeating the same procedure multiple times can be avoided. Torres et al. recently found early onset of pain relief to result in greater patient satisfaction [27]. This minimizes uncomfortable positioning of the patient and avoids delays in the procedures. Furthermore, patients without pain cooperate in the process, making it safer and accurate. While further studies involving different fentanyl preparations are designed and carried out, the results of the present study have shown that FPNS might be a good option to relieve incidental breakthrough pain in cancer patients describing moderate to intense pain during necessary procedures in the context of radiotherapy.

Regarding the secondary endpoints, the dose most frequently required to achieve the objective of a 50% decrease in NRS score was 100–200 µg of FPNS. However, patients receiving high morphine doses may require higher doses. Pain relief has been effective and quick, with easy FPNS administration. The mean time to achieve a breakthrough pain reduction of at least 50% was 15.5 min. It is commonly accepted that an ≥ 2 point reduction in pain intensity is an indicator of clinically meaningful response [28]. In our study we needed to be restrictive and therefore did not start a procedure until we achieved a 50% reduction of the NRS score (6 points of NRS reduction were recorded in our study within a mean time of 15.5 min). The observable rapid response is probably due to the bioavailability of the FPNS formulation [22]. Fentanyl is a lipophilic opioid and has shown very rapid mucosal absorption, thus making it a good analgesic for breakthrough pain. In our study, the onset of action of FPNS took place in less than 5 min in almost 50% of the patients. The primary objective of a 50% NRS reduction was achieved in less than 15 min in almost 70% of the treated patients (Fig. 3). These results have been shown to be statistically significant, and support the results obtained in a randomized, double-blind, crossover study in which the efficacy and tolerability of FPNS was assessed in 114 patients – documenting significant improvement of the pain intensity scores within as early as 5 min ($p < 0.05$) [25]. In our study of 26 treated patients, the average time to onset of action was 7 min (range 3–15 min). The nasal tissues are highly vascularized, have good permeability, and avoid first-pass metabolism

in the liver [29,30]. For patients with breakthrough pain, the nasal route may be particularly beneficial and lead to higher acceptability [7,28].

FPNS toxicity seems to be predictable and comparable to that of other quick-release opioid drugs [11]. One of the patients dropped out of the trial due to intense dizziness and nausea, and 7 described tolerable symptoms. In most of the patients FPNS was well tolerated (>73% of the cases), and no complications related to nasal administration were recorded.

Finally, the cost utility analysis showed a gain in health-related quality of life, decreasing the pain and the economic cost per patient (Table 5). Furthermore, relief from pain facilitates the Department workflow and reduces costs associated with clinical delays. Radiotherapy costs are predominantly determined by personnel and equipment [31]. By preventing unnecessary delays we also maintain Department productivity. Therefore, pain control in our patients before radiotherapy procedures are carried out is not only a very efficient and low-cost process but also affords more health-related quality-adjusted life years for the patients.

5. Conclusions

Certain necessary procedures and manoeuvres in radiotherapy may cause moderate to severe breakthrough pain. A simple, rapid and strong analgesic is needed in such situations. FPNS offers rapid absorption and analgesia. It is particularly efficient and well accepted by radiotherapy patients. Such relief allows the necessary procedures to be completed accurately, without additional needless suffering for patients, and maintaining the Radiotherapy Department productivity. FPNS was well tolerated, and no major complications were observed related to intranasal administration. However, further studies and clinical trials are needed to formally assess the comparative tolerability and efficacy of the different opioid preparations, in order to help place the results of this efficacy analysis within a wider clinical context.

Conflict of interest

There are no known conflicts of interest associated to this publication, and there has been no financial support for this work that could have influenced its outcome.

Ethical aspects

Ethical committee approval: keeping in mind the aetiology of this type of pain, the survey was approved by the Ethic Committees.

Patient information: patients were informed and accepted the fentanyl pectin nasal spray administration. Written informed consent was obtained from all patients according to the guidelines for Good Clinical Practice.

Acknowledgments

Not applicable. There are no contributions that need acknowledging.

References

- [1] Luther W, Brady, Theodore E, Yaeger, editors. *Encyclopedia of Radiation Oncology*. Springer; 2013.
- [2] Portenoy R-K, Forbes K, Lussier D, Hanks G. Difficult pain problems: an integrated approach. In: Doyle D, Hanks G, Cherny N, Calman K, editors. *Oxford Textbook of Palliative Medicine*. 3rd ed. Oxford: Oxford University Press; 2004. p. 438–58.
- [3] Portenoy RK, Hagen NA. Breakthrough pain definition and characteristics. *Pain* 1990;41:273–81.
- [4] Gómez-Batiste X, Madrid F, Moreno F, Gracia A, Trelis J, Nabal M, Alcalde R, Planas J, Camell H. Breakthrough cancer pain: prevalence and characteristics in patients in Catalonia, Spain. *J Pain Symptom Manage* 2002;24:45–52.
- [5] Mercadante S, Radbruch L, Caraceni A, Cherny N, Kaasa S, Nauck F, Ripamonti C, De Conno F. Steering Committee of the European Association for Palliative Care (EAPC) Research Network. Episodic (Breakthrough) pain: consensus conference on an expert working group of the European Association for Palliative Care. *Cancer* 2002;94:832–9.
- [6] http://en.wikipedia.org/wiki/IMS_Health.
- [7] Fallon M, Reale C, Davies A, Lux AE, Kumar K, Stachowiak A, Galvez R, Fentanyl Nasal Spray Study 044 Investigators Group. Efficacy, safety and patient acceptability of fentanyl pectin nasal spray compared with immediate-release morphine sulphate tablets in the treatment of breakthrough cancer pain: a multicentre, double-blind, double-dummy, multiplecrossover study. *J Support Oncol* 2011;9:224–31.
- [8] Zeppetella G, Davies A, Eijgelshoven I, Jansen JP. A network meta-analysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes. *J Pain Symptom Manage* 2013;24, pii: S0885–3924(13)00365–5.
- [9] Portenoy RK, Raffaelli W, Torres LM, Sitte T, Deka AC, Herrera IG, Wallace MS, Fentanyl Nasal Spray Study 045 Investigators Group, Fentanyl Nasal spray Study 045 Investigators Group. Long-term safety, tolerability, and consistency of effect of fentanyl pectin nasal spray for breakthrough cancer pain in opioid-tolerant patients. *J Opioid Manag* 2010;6:319–28.
- [10] Davies A, Sitte T, Elsner F, Reale C, Espinosa J, Brooks D, Fallon M. Consistency of efficacy, patient acceptability, and nasal tolerability of fentanyl pectin nasal spray compared with immediate-release morphine sulfate in breakthrough cancer pain. *J Pain Symptom Manage* 2011;4:358–66.
- [11] Fisher A, Watling M, Smith A, Knight A. Pharmacokinetics and relative bioavailability of fentanyl pectin nasal spray 100–800 µg in healthy volunteers. *Int J Clin Pharmacol Ther* 2010;48:860–7.
- [12] Watts P, Smith A. PecSys: in situ gelling system for optimised nasal drug delivery. *Expert Opin Drug Deliv* 2009;6:543–52.
- [13] Blanco B, García Ruiz AJ, García-Agüa Soler N. Resultados en salud y eficiencia del fentanilo intranasal en pectina en el dolor irruptivo en la práctica clínica habitual. *Rev Soc Esp Dolor* 2013;20:221–9.
- [14] Zeppetella G, Davies A-N. Opioids for the management of breakthrough pain in cancer patients. *Cochrane Database Syst Rev* 2013;21:CD004311, <http://dx.doi.org/10.1002/14651858.CD004311.pub3>.
- [15] Zeppetella G. Evidence-based treatment of cancer-related breakthrough pain with opioids. *J Natl Compr Cancer Netw* 2013;11:S37–43.
- [16] Taylor D, Radbruch L, Revnic J, Torres LM, Ellershaw JE, Perelman M. A report on the long-term use of fentanyl pectin nasal spray in patients with recurrent breakthrough. *Pain* 2013, pii: S0885–3924(13)00480–6.
- [17] Bell BC, Butler EB. Management of predictable pain using fentanyl pectin nasal spray in patients undergoing radiotherapy. *J Pain Res* 2013;11:843–8.
- [18] Actiq, summary of product characteristics. <http://www.aemps.gob.es/CIMA>. Product property of Teva UK Limited.
- [19] Effentora, summary of product characteristics. <http://www.aemps.gob.es/CIMA>. Product property of Teva Europe.
- [20] Abstral, summary of product characteristics. <http://www.aemps.gob.es/CIMA>. Product property of Prostrakan Limited.
- [21] PecFent, summary of product characteristics. <http://www.aemps.gob.es/CIMA>.
- [22] Mercadante S. Pharmacotherapy for breakthrough cancer pain. *Drugs* 2012;72:191.
- [23] Oddershede L, Andreasen JJ, Ehlers L. Estimation of utility values from numeric rating scale measures of health in patients undergoing cardiac surgery. *Clin Econ Outcomes Res* 2014;6:21–7.
- [24] Farrar John T, Portenoy Russell K, Berlin Jesse A, Kinman Judith L, Strom Brian L. Defining the clinically important difference in pain outcome measures. *Pain* 2000;88:287–94.
- [25] Portenoy RK, Burton AW, Gabrail N, Taylor D, Fentanyl Pectin Nasal Spray 043 Study Group. A multicenter, placebo-controlled, double-blind, multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain. *Pain* 2010;151:617–24.
- [26] Radbruch L, Torres LM, Ellershaw JE, Gatti A, Luis Lerzo G, Revnic J, Taylor D. Long-term tolerability, efficacy and acceptability of fentanyl pectin nasal spray for breakthrough cancer pain. *Support Care Cancer* 2012;20:565–73.
- [27] Torres LM, Revnic J, Knight AD, Perelman M. Relationship between onset of pain relief and patient satisfaction with fentanyl pectin nasal spray for breakthrough pain in cancer. *J Palliat Med* 2014;17:1150–7.
- [28] Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. *J Pain Symptom Manage* 2003;25:406.
- [29] Dale O, Hjortkjaer R, Kharasch ED. Nasal administration of opioids for pain management in adults. *Acta Anaesthesiol Scand* 2002;46:759–70.
- [30] Illum L. Nasal drug delivery-possibilities, problems and solutions. *J Control Release* 2003;87:187–98.
- [31] Lievens Y, van den Bogaert W, Kesteloot K. Activity-based costing: a practical model for cost calculation in radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;57:522–35.