INTRODUCTION

Pain is the dominant symptom in 70% of patients with advanced cancer and in approximately 50% of patients who receive anticancer treatment\(^1\). The physical causes of pain in the cancer patient are related to the tumor, such as pain caused by nerve compression, soft-tissue infiltration or edema; related to the antineoplastic treatment, such as postoperative pain or pain caused by mucositis; or related to concurrent complications, such as osteoporosis, constipation and pressure sores. Psychological and psychosocial factors may add to the physical component, resulting in a general pain syndrome. Oral analgesia remains the first-line treatment in pain control, with opioids being the standard therapy for moderate to severe pain. However, certain clinical situations may make oral anal-

ORIGINALES

Prospective clinical evaluation of transdermal fentanyl for the treatment of cancer pain

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BACKGROUND: Transdermal therapeutic systems offer potential advantages over oral or intravenous routes of drug administration. The purpose of this prospective study was to evaluate the analgesic efficacy of the new drug formulation transdermal fentanyl (TTS Fen) in the treatment of cancer pain, as well as its safety and patient acceptability.

METHODS: Forty patients were included over a 12-month period. The dose of TTS Fen was titrated individually, increasing 25 µg/h every 72 hours, until analgesic control was adequate.

RESULTS: Pain intensity, determined by means of a numeric analog scale going from 0 to 10, decreased from a mean of 7.14 on day 1 of treatment to 3.96 on day 15, 2.40 on day 60 and 2.07 on day 90, with significant differences (\(p = 0.002\)). Treatment satisfaction was high in 89% of patients. Rescue medication with short-acting oral morphine was needed in 30% of patients during the first week of treatment with TTS Fen, but only in 26% and 15% of patients by days 15 and 60, respectively. The most frequent side effects were constipation, which occurred in 39% of patients, drowsiness in 21% and fatigue in 13%.

CONCLUSIONS: TTS Fen is effective in the treatment of cancer pain and patient satisfaction is high, mainly because of ease of use. The frequency of side effects is low.

Key words: Cancer pain. Transdermal fentanyl. Opioid analgesics.


Evaluación clínica prospectiva del fentanilo transdérmico en el tratamiento del dolor oncológico

FUNDAMENTO: La vía transdérmica de administración de fármacos presenta ventajas potenciales sobre las vías oral o parenteral. El objetivo de este estudio prospectivo fue evaluar la eficacia analgésica del nuevo fármaco fentanilo transdérmico (Fen TTS) en el control del dolor neoplásico, su seguridad y la satisfacción global del paciente.

MÉTODOS: En un periodo de 12 meses se incluyeron 40 pacientes. La dosis de Fen TTS fue ajustada individualmente, aumentando 25 µg/h cada 5 días hasta lograr un control analgésico adecuado.

RESULTADOS: La intensidad del dolor, según una escala analógica numérica de 0 a 10, descendió de una media de 7.14 el día 1 del tratamiento a 3.96 el día 15, 2.40 el día 60 y 2.07 el día 90, siendo significativas las diferencias (\(p = 0.002\)). La satisfacción con el tratamiento fue alta en el 89% de los pacientes. El 50% de los pacientes precisó analgesia de rescate con morfina oral de liberación rápida la primera semana de tratamiento, disminuyendo al 26 y al 15% los días 15 y 60, respectivamente. Los efectos secundarios más frecuentes fueron estreñimiento, 39%, somnolencia, 21% y astenia, 13%.

CONCLUSIONES: El Fen TTS es eficaz en el tratamiento del dolor neoplásico y su aceptación por el paciente es alta, principalmente por la comodidad de administración. Los efectos secundarios son leves.

Palabras clave: Dolor oncológico. Fentanilo transdérmico. Analgésicos opiáceos.

INTRODUCTION

Pain is the dominant symptom in 70% of patients with advanced cancer and in approximately 50% of patients who receive anticancer treatment\(^1\). The physical causes of pain in the cancer patient are related to the tumor, such as pain caused by nerve compression, soft-tissue infiltration or edema; related to the antineoplastic treatment, such as postoperative pain or pain caused by mucositis; or related to concurrent complications, such as osteoporosis, constipation and pressure sores. Psychological and psychosocial factors may add to the physical component, resulting in a general pain syndrome. Oral analgesia remains the first-line treatment in pain control, with opioids being the standard therapy for moderate to severe pain. However, certain clinical situations may make oral anal-

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Fentanyl is a synthetic phenylpiperidine opioid incorporated in an adhesive patch known as the transdermal therapeutic system (TTS). The TTS releases fentanyl into the skin beneath the patch, forming a reservoir in the upper skin layers. The amount of active drug released is proportional to the size of the patch and is consistent with subsequent blood concentrations of fentanyl. Each application gives pain relief for approximately 3 days, and the patch is then replaced. In bioavailability studies, 92% of a fentanyl dose in the TTS reached the systemic circulation as unchanged fentanyl. The concentration curve of fentanyl has three phases: latency, balance and removal. After the first application of the patch, the blood level of fentanyl increases gradually until a maximum which remains stable between 12 and 24 hours, and then slowly decreases during the following 48 hours.

Fentanyl is a potent opioid analgesic with high affinity and selectivity for pain receptors in the central nervous system. The efficacy of TTS fentanyl in the treatment of cancer-related pain has been already demonstrated in previous studies. However, it is relatively new to the market in Spain and is currently undergoing clinical evaluation. The objective of this study was to prospectively evaluate the efficacy and safety of TTS fentanyl in the long-term treatment of cancer pain, as well as patient satisfaction with the medication.

PATIENTS AND METHODS

Patients

During a 12-month period, 40 patients with a diagnosis of cancer of any site were included in the study. Inclusion criteria were: age ≥ 18 years, radiotherapy treatment at present or in the past, and pain requiring strong opioid analgesics. The following exclusion criteria were adopted: severe hepatic or renal impairment (serum total bilirubin > 50 mmol l⁻¹ or serum creatinine more than 1.5 times the normal upper limit of the reference range), severe pulmonary or heart disease or impaired level of consciousness.

Drug administration and procedure

In patients who presented with severe cancer pain which had not been previously treated, TTS fentanyl (Durogesic®, Janssen-Cilag), 25 µg/h, was prescribed. Similarly, patients on treatment with maximum doses of weak opioids and insufficient pain control were started on patches of TTS Fen. 25 µg/h. In both cases short-acting oral morphine (Sevedol®, Asta Medica) was prescribed during titration of the dose of TTS Fen at the start of the study and to provide analgesia for breakthrough pain throughout the period of treatment.

Adjuvant treatments such as nonsteroid anti-inflammatory drugs (NSAIDs) and antidepressants were also permitted. Patients on treatment with sustained-release oral morphine were shifted to TTS Fen, calculating the starting dose of TTS Fen according to the conversion tables of Donner et al. As a practical rule, the total 24 h morphine requirement was divided by two, for instance, 120 mg of MST²/day/2 = 50 µg/h patches of TTS Fen. Short-acting oral morphine was prescribed as rescue medication.

The fentanyl patch was applied to a hair-free area of the upper thorax and then replaced after 72 h, generally at home. Pain intensity was assessed every 72 h during the first week of treatment or until total pain control was achieved, and on days 15, 30, 60 and 90 thereafter. Doses of TTS Fen were adjusted according to pain scores and to the amount of supplementary short-acting morphine required for breakthrough pain.

Throughout the study, patients kept daily diaries recording estimated pain intensity and use of concomitant medication. A visual analogue scale (VAS) ranging from 0 to 10 (0 = no pain, 10 = worst imaginable pain) was used by the patient and by the clinical investigator in the consecutive evaluations. The sleep pattern was evaluated according to a four-point questionnaire: 1 = sleeps well, 2 = frequently wakes up, 3 = unable to sleep, 4 = needs hypnotics. Patients were asked about satisfaction with treatment (from highly satisfied to slightly satisfied or not satisfied), and what they valued most, the analgesic effect or ease of use. Side effects and ECOG performance status were also recorded by investigators at each visit.

Statistical analysis

In order to estimate changes in pain control and sleep capacity, arithmetic means, standard deviations and ranges were calculated for statistical analysis. VAS scores for pain intensity on days 1, 15, 60 and 90 were compared by means of Friedman’s test, defining the level of significance as p ≤ 0.05.

RESULTS

Forty patients were entered into the study. Two patients refused the prescribed treatment because of fear of using strong opioids. The characteristics of the 38 remaining patients are shown in table 2. Thirty-three patients had nociceptive pain of long-term duration (> 1 month). Palliative radiation therapy

<table>
<thead>
<tr>
<th>Oral morphine (mg/day)</th>
<th>TTS fentanyl (µg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-90</td>
<td>25</td>
</tr>
<tr>
<td>91-150</td>
<td>50</td>
</tr>
<tr>
<td>151-210</td>
<td>75</td>
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<td>211-270</td>
<td>100</td>
</tr>
<tr>
<td>271-330</td>
<td>125</td>
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<td>331-390</td>
<td>150</td>
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<td>391-450</td>
<td>175</td>
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<td>451-510</td>
<td>200</td>
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<td>511-570</td>
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<td>571-630</td>
<td>250</td>
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<tr>
<td>631-690</td>
<td>275</td>
</tr>
<tr>
<td>Every additional 60 mg</td>
<td>+ 25</td>
</tr>
</tbody>
</table>

TABLE 1. Conversion table from sustained-release oral morphine to TTS Fentanyl

1.160