

3012

POSTER

Review of the Pharmacokinetic Profile of Fentanyl Transmucosal Formulations

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Background: Breakthrough pain (BTP) is a transitory flare of moderate-to-severe pain that occurs in patients with otherwise stable, controlled persistent pain. There are intra and inter-individual variations with BTP, including time to peak intensity from one second to 30 minutes and duration of pain from one minute up to several hours. Drug delivery technologies allowed the development of new fentanyl formulations: rapid-onset opioids with pharmacokinetic profiles more consistent with BTP episodes with faster onset of analgesia than traditional short acting opioids. There are 2 routes of transmucosal administration: oral or nasal. Among the oral routes: Actiq[®] (oral transmucosal fentanyl citrate [OTFC]) is via swabbing, Effentora[®] (fentanyl buccal tablet [FBT]) used buccally or sublingually with an active OraVescent[®] technology to enhance local fentanyl absorption, Abstral[®] (sublingual fentanyl [SLF]) is administered sublingually with a rapid dissolution and a passive absorption and Breakly[®] (fentanyl buccal soluble film [FBSF]) is administered buccally via a film. Among the nasal routes: Instanyl[®] (intranasal fentanyl spray [INFS]) that flushes in passively and PecFent[®] (fentanyl pectin nasal spray [FPNS]) utilizes a gel-based formulation. Pharmacokinetic features differentiate these formulations.

Material: For this review, 3 available formulations were evaluated as representatives: OTFC, FBT and INFS. For comparison purposes similar C_{max} ranges (0.7–0.95 ng/mL) were selected.

Results: Plasma concentration increases: up to 60' for OTFC, rapidly up to 30' and sustained through 60' for FBT, up to 15' and decrease rapidly thereafter for INFS. Compared to FBT and INFS, the early increase in plasma fentanyl concentration with OTFC is more gradual. The plasma fentanyl concentration is maintained through 60 minutes with FBT and OTFC but declines rapidly with INFS. The elimination phase of fentanyl depends solely on the molecule (i.e., it is the same regardless of the delivery system).

Conclusion: It is important to consider the pharmacokinetic profile of each formulation along with clinical data when physicians are selecting a rapid-onset opioid for a patient. Given the substantial variability of BTP experienced by patients, these pharmacokinetic differences may provide useful information for physicians.

3013

POSTER

A Pan-European Phase IV Open-label Multicentre Study in Patients With Breakthrough Cancer Pain (BTcP) Treated With Fentanyl Buccal Tablet (FBT) – Preliminary Data From Germany

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Background: FBT treats BTcP in adult patients receiving opioid maintenance therapy. This study (EudraCT number: 2008–001841–24) was designed to compare the percentage of patients reaching an effective FBT dose when starting titration at 100 µg vs 200 µg and secondary objectives were to measure the efficacy and safety of FBT.

Methods: After the screening period, patients were enrolled in an open-label randomized titration period (patients titrated FBT starting at 100 or 200 µg up to a successful dose [100, 200, 400, 600, 800 µg maximum]) followed by an open-label treatment period (treatment up to 8 BTcP episodes at the successful dose). The patient inclusion criteria followed the SmPC for FBT. The preliminary data of the patients enrolled in Germany (n=90) are presented with BTcP characteristics as well as patients' assessment of FBT treatment.

Results: Breast cancer was the most frequent primary tumour (26.7%; 70% out-patients (63/90)). The patients had a mean overall pain intensity=5.4±2.4 on a 0–10 NS, 71.8% (56/78) of the patients reported 1–3 BTcP episodes per day, at enrolment. The average time from onset to peak intensity was within 10 minutes for 48.7% of the patients (38/78), from 10 to 30 minutes for 38.5% (30/78) and more than 30 minutes for 12.8% (10/78). After titration, the percentage of patients achieving a successful dose of FBT at 100, 200, 400, 600 and 800 µg was 25%, 42%, 23%, 8% and 2% respectively. Patients' quality of life and functional status improved after treatment with FBT (Brief Pain Inventory-7 item subscale). FBT was assessed as very easy-easy/convenient for treating BTcP by 72.7% (32/44) of the patients. The patient satisfaction was in favour of FBT.

Conclusions: These preliminary data from Germany on BTcP episodes characterization are consistent with previous published studies. The majority of the patients found FBT convenient to use. Final results from the study will provide information on the optimal starting dose, the safety, and the efficacy of FBT; it will also offer information on BTcP characterizations & treatments in real clinical practice.

3014

POSTER

Medical and Nursing Interventions in Hospitals in the Last Days of Life of Cancer Patients in Italy and the Netherlands

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Background: International variation in end-of-life care is known to be present. More insight in current practices in different countries makes it possible to discuss this variation in order to improve end-of-life care in general. This study aims to describe medical and nursing interventions in hospitals for dying cancer patients in Italy and the Netherlands.

Method: Medical records were scrutinized using a checklist of medical and nursing interventions, such as anti-cancer treatments, invasive interventions, non-invasive interventions, diagnostics and nutrition and hydration. In Italy consecutive deceased cancer patients of three general medicine wards of a general hospital (n=59) were included. In the Netherlands 38 cancer patients who consecutively deceased at one of 9 different wards of a university hospital were included. All patients had to have been admitted in the hospital for at least 3 days.

Results: In the last days of life only 2 Italian patients received anti cancer treatments and in both countries no patients received invasive interventions like dialyses, invasive inhalation or resuscitation.

Patient characteristics and most often applied interventions

	Number of patients (%)			
	Italy (n = 59)		Netherlands (n = 38)	
	Day 3 before death	Day of death	48–72 h before death	0–24 h before death
Age, mean	74	61		
Admission duration, mean (median)	20 (15)	19 (9)		
Interventions				
Therapeutic drainage	0 (0)	0 (0)	10 (26)	7 (18)
Central venous access	9 (15)	9 (15)	n/k	n/k
Urinary catheter	36 (61)	41 (70)	14 (37)	19 (50)
Oxygen inhalation	18 (31)	23 (39)	18 (51)	22 (58)
Diagnostics				
Blood test	19 (32)	6 (10)	21 (55)	13 (34)*
Oxygen saturation	n/k	n/k	30 (79)	20 (53)*
ECG	2 (3)	2 (3)	9 (24)	5 (13)
Diagnostic radiology	1 (2)	0 (0)	17 (45)	5 (13)*
Nutrition and hydration				
TPN	14 (24)	10 (17)	1 (3)	0 (0)
Nasogastric tube	0 (0)	0 (0)	7 (18)	2 (5)*
Liquids (hydration)	43 (73)	29 (49)*	18 (51)	15 (40)*

n/k, not known.

*Significant difference between day 3 and day of death, p-value <0.05.

Conclusion: In Italy and the Netherlands diagnostics are rather common in the last days of life, especially in the Netherlands. We found few changes in interventions during the last three days of life, except a decrease of artificial hydration in both countries and a decrease in diagnostics and artificial nutrition in the Netherlands.

3015

POSTER

The Associates of the Risk of Febrile Neutropenia After Conventional Dose Chemotherapy in Patients With Common Cancers – a Prospective Study From Two Tertiary Centers

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Aim: Febrile neutropenia (FN) is a life threatening complication of cancer chemotherapy. However, homogenous risk models for FN solely in solid tumours, is still not frequently reported and validated. In this prospective

study, we aimed to form a risk model in patients with common cancers by also questioning the role of various biochemical markers in this regard.

Materials and Methods: During a period of 8 months between May 2010 and January 2011, consecutive patients were prospectively recruited from 2 tertiary cancer centers. Ethical committee approval was obtained prior to onset of the study. Patients only with breast, colorectal and lung cancers, and all stages of disease, were allowed. Data on disease and treatment characteristics as well as comorbidities, global quality of life scores as assessed by EORTC QLQ-C30 questionnaires, biochemical and hematological parameters (serum creatinine, Lactate Dehydrogenase, creatinine, ALT, albumin, hemoglobin, monocyte, neutrophil, lymphocyte, thrombocyte counts, mean platelet volume, and C reactive protein levels (CRP)), and Granulocyte Colony Stimulatory Factor (G-CSF) usage were collected. Patients were carefully observed for the development of FN after each chemotherapy cycle. Univariate and multivariate logistic regression tests are conducted to test the determinants of FN.

Results: A total of 1139 patients were recruited and 3970 cycles were delivered during the study period. The number of cycles delivered for patients with breast, lung and colorectal cancers are 1608 (40.5%), 1023 (25.8%), and 1339 (33.7%), respectively. In total, 59 episodes of FN (after 1.5% of total cycles) in 53 patients are encountered. Mortality occurred in only one case after FN (~2% mortality in patients with FN). As, type of cancer was associated with the risk of FN (lung cancer versus breast and colorectal cancer), data was separately analyzed for these 2 groups. In patients with breast and colorectal cancers, the independent predictors of FN were cycle of chemotherapy (Exp(B)=0.8, P=0.045), gender (Exp(B)=5.2, P=0.030) and previous history of FN (Exp(B)=282.5, P<0.001). On the other hand, in patients with lung cancer, the independent determinants were the site of chemotherapy administration (inpatient versus outpatient, Exp(B)=52.6, P=0.001), CRP levels (Exp(B)=3.1, P=0.038), and again, previous history of FN (Exp(B)=81.6, P<0.001).

Conclusions: In patients with common cancers and in daily practice, type of cancer is important as different predictors of FN seem to be influential. Notably, CRP levels and gender appear to be predictive. Some of the predictors from this study are novel, and can well help stratify patients according to their FN risk. We are working to produce a handy nomogram to be used by the clinicians. In addition, we are starting to test our model in a new cohort of patients for validation purposes.

3016

POSTER

Clinical Differences of Opioids in Cancer Pain not Responding to Fentanyl Escalation

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Background: Basically morphine, oxycodone and fentanyl are considered to have similar therapeutic efficacy against cancer pain, however we often experience different pharmacological responses between these opioids. Few patients obtain insufficient analgesic response despite the dose escalation of fentanyl. The aims of this study were describe patients with poor analgesic responses and to evaluate the efficacy of opioid rotation from fentanyl to other opioid.

Methods: This was a retrospective chart review in 224 patients who requested consultation with the palliative care team at the Teikyo Oncology Center in Tokyo from Jan. 2010 to Dec. 2010, including 20 patients were administered fentanyl. Four patients were enrolled with poorly controlled cancer related pain [worst pain severity rated as 7 or greater on the Numeric Rating Scale (NRS)] and required opioid rotations (OR). They did not have any cancer therapies and medications concerning to reduce their pain within two weeks. Pain intensity, safety profile and opioid daily dose at baseline and after opioid rotation were evaluated on each patient.

Results: Pain intensity measured with NRS was markedly decreased after opioid rotation in every patient. Effective daily doses were varied from 6 to 50% lower than general equianalgesic doses of fentanyl.

Conclusions: These results showed opioid conversion ratio varies widely and suggest fentanyl-induced hyperalgesia and tolerance. Opioid rotation is considered the effective method to improve refractory pain, but the conversion dose should be titrated carefully based on opioids condition.

Patient	Fentanyl		Route	Adjuvant analgesics	Duration	Opioid rotation (OR)			NRS post OR
	Dose					NRS pre OR	Opioid post OR	Dose of opioid post OR	
1	67 µg/h (iv)	iv		ketamin	10d	8	Morphine (oral)	30 mg	0
2	100 µg/h (td)	td		pregabalin	2M	9	Morphine (oral)	120 mg	2
3	300 µg/h (td)	td		gabapentin	3M	8	Oxycodone(oral)	30 mg	0
4	100 µg/h (td)	td		gabapentin	2M	8	Morphine (iv)	10 mg	1

iv: intravenous; td: transdermal.

3017

POSTER

Management of Chemotherapy-induced Neuropathy With 8% Capsaicin Patch – a Preliminary Case Series

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Chemotherapy-induced painful peripheral neuropathy is a known sequelae following treatment with agents like bortezomib, vincristine, taxols and platinum compounds. Systemic neuropathic agents and opioids have been used in its management, but adequate analgesia is not always achieved despite maximal therapy and dose escalation of opioids could be limited by unacceptable side effects. We are presenting our preliminary case series of ten patients with resistant chemotherapy-induced neuropathy who we have successfully managed using 8% capsaicin patch.

10 patients who had painful chemotherapy-induced peripheral neuropathy were treated with a single 30-minute application of 8% capsaicin patch after an hours' pre-treatment with EMLA as local anesthetic cream. The treatment was well tolerated and the burning sensation after treatment was managed with local cooling measures or small doses of short-acting opioids. Side effects like erythema, pruritus and pain were essentially at the patch application site and were self-limiting. Patients started reporting improvement in pain relief after about 24 hours and most patients reported sustained analgesia on follow-up. There was consistent reduction in pain scores and improvement in activities like walking that were previously limited by the pain. The pain relief was further validated by reduction in opioid doses and also systemic neuropathic pain medications.

Capsaicin acts on the TRPV1 receptors and an 8% capsaicin patch is being recently used for the management of peripheral neuropathic pain states. The mechanism of action is by initial hyperstimulation and then neurite degeneration; this is followed by regeneration over three to six months. There is good analgesic effect, but no change in sensory modalities like light touch, pinprick, temperature or vibration sense. Unlike the 0.075% capsaicin cream, which needs to be applied three or four times a day over several weeks, the 8% patch is a single application and could be repeated after 3 months.

Preliminary findings are very encouraging in the use of 8% capsaicin patches in the management of chemotherapy-induced neuropathy. It is efficacious, well tolerated and could reduce systemic analgesic requirements. Further studies and long-term follow-up are being carried out to further evaluate this novel therapy in the management of chemotherapy-induced painful peripheral neuropathy.

3018

POSTER

Treatment of Painful Bone Metastases With Magnetic Resonance Guided Focused Ultrasound

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Background: Magnetic Resonance guided Focused Ultrasound (MRgFUS) is a non-invasive treatment technique that recently has been shown to be effective for thermal ablation of a variety of benign and malignant tumours. We present here results of a clinical trial conducted in our facility. The main objective of the trial was to evaluate safety and effectiveness of MRgFUS treatment of pain caused by bone metastases.

Material and Methods: 31 patients with painful bone metastases were treated with MRgFUS at Petrov Research Institute of Oncology, St. Petersburg, Russia. Immediately after procedure patients were examined for any adverse events and after a brief recovery discharged. Patients were followed up on 1 and 3 days, 1 and 2 weeks, 1, 2 and 3 months post treatment. During each visit, treatment safety was evaluated by recording and assessment of device or procedure related adverse events. Effectiveness of palliation was evaluated using the standard pain scale (0-no pain/10-worst pain imaginable) and by monitoring changes in the intake of pain-relieving medications. A reduction of 2 points or more on pain scale was considered a significant response to treatment. 17 patients were male and 14 female. Mean age was 55 years old (19–76). The primary cancers were: 19 breast, 4 stomach, 2 bronchus, 2 bladder, 4 other. Targeted lesions were 14 osteolytic, 8 osteoblastic and 9 mixed. 23 were pelvis metastases, 4 were located in the humerus bone and 4 were located in the ribs.

Results: No significant device or procedure related adverse events were recorded. 3 patients died during the follow-up period due to disease progression, thus 3 months follow-up data includes only results of 28 patients. All patients reported significant improvement in pain with no change in their medication intake. Mean worst pain score at baseline, 1 day, 3 days, 1 week, 2 weeks, 1, 2 and 3 months post-treatment was 6.9, 6.1, 5.1, 3.5, 2.6, 1.8, 1.2 and 0.9 respectively.

Conclusions: MRgFUS can provide effective, safe and noninvasive palliative therapy for patients suffering from painful bone metastases.