Fentanyl

Statut de médicament essentiel ✓

Section: 2. Medicines for pain and palliative care > 2.2. Opioid analgesics

Codes ATC: N01AH01

Indication	Chronic cancer pain Code ICD11: ML00.10
INN	Fentanyl
Type de médicament	Chemical agent
Type de liste	Liste de base
Additional notes	*For the management of cancer pain
Formulations	Local > Topical > Transdermal patch: 12 µg/hour ; 25 µg/hour ; 50 µg/hour ; 75 µg/hour ; 100 µg/hour
Historique des statuts LME	Ajouté pour la première fois en 2017 (TRS 1006)
Sexe	Tous
Âge	Adolescents et adultes
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.
Balises	Cancer
Wikipédia	Fentanyl
DrugBank	Fentanyl

Recommandation du comité d'experts

The Expert Committee accepted that there is a need for additional opioid options for treatment of pain in cancer patients. The Committee therefore recommended the addition of transdermal fentanyl to the EML for treatment of cancer pain. The Committee did not recommend transdermal fentanyl for inclusion on the EMLc because of adverse effects and concerns regarding overdosing. The Committee noted the potential for harms, misuse and abuse associated with residual fentanyl in used patches and appropriate, safe disposal of used patches is essential.

Contexte

Fentanyl has not previously been considered for inclusion on the EML/EMLc. Opioid analgesics included on the EML are codeine and morphine. Only morphine is listed on the EMLc. Hydromorphone and oxycodone are considered alternatives to morphine under a square box listing.

Pertinence pour la santé publique

Cancer is one of the leading causes of morbidity worldwide, with approximately 14 million new cases in 2012 (1). Pain is a frequent and debilitating feature of cancer, occurring across all phases from diagnosis to palliation (2, 3). It is estimated that 31.8% of patients with cancer are undertreated for pain (4). Opioid therapy is the cornerstone of cancer pain management. The burden of cancer is particularly high in low- and middle-income countries, where 70% of deaths from cancer occur. Patients living in these countries often have limited access to morphine, which is the strong opioid of choice for management of moderate to severe cancer

pain. This application proposed fentanyl as a treatment alternative to morphine to help increase access to opioid pain relief for cancer patients.

Bénéfices

Fentanyl is a potent synthetic opioid that is suitable for transdermal administration and may provide a useful alternative to morphine for patients with cancer pain. It may be particularly useful for patients unable to take or tolerate oral opioids (e.g. because of malabsorption, dysphagia, vomiting or severe constipation) (5) and in patients with renal impairment. The application presented the findings of a search of the literature published since 2012 on transdermal fentanyl and cancer pain. Only one randomized trial was identified, which compared transdermal fentanyl and pregabalin for neuropathic cancer pain (6). A 2013 Cochrane systematic review of nine trials involving 1244 patients assessed the analgesic efficacy and adverse effects of transdermal fentanyl for moderate to severe cancer pain (7). The quality of evidence in the included studies was limited, with small numbers and failure to report clinically relevant outcomes. However, the findings of the review led the authors to conclude that, for patients able to tolerate treatment and remain in the study until its end and where data were reported, pain was improved within a short time period and the majority had "no worse than mild pain". Lower rates of constipation were observed with transdermal fentanyl compared with sustained-release morphine (risk ratio (RR) 0.61; 95% CI 0.47–0.78). A systematic review (8) of randomized trials on the effectiveness of opioids for cancer pain in which pain relief was the primary outcome measure concluded that there was fair evidence for the efficacy of transdermal fentanyl, based on a single RCT of fentanyl versus paracetamol plus codeine for management of metastatic bone pain (9). Use of transdermal fentanyl in 64 paediatric (age 2–14 years), opioid-naive cancer patients was analysed in a prospective open-label study (10). There was significant improvement in scores on both the visual analogue scale (from 6.82 at baseline to 1.18 by day 15) and FACES pain rating scale (from 6.13 at baseline to 1.13 by day 15). No significant side-effects were reported and the authors concluded that transdermal fentanyl was an effective, safe and well-tolerated treatment for paediatric cancer patients.

Torts

Common adverse effects associated with opioid therapy are also seen with fentanyl, including respiratory effects, nausea, vomiting, constipation and somnolence. Rash, application site reactions and itch have also been reported with the transdermal formulation (5). Transdermal fentanyl may cause less constipation than oral morphine (7). Severe diarrhoea associated with transdermal fentanyl during the first 72 hours of treatment has been reported (11).

Preuves supplémentaires

Transdermal fentanyl and sustained-release oral morphine were compared in opioid-naive patients with moderate to severe cancer pain and in opioid-experienced patients with mild to moderate pain (12). The two drugs showed equal efficacy in terms of pain control and improved sleep quality. Fentanyl was better tolerated than morphine, with fewer fentanyl-treated patients reporting constipation or discontinuing the trial. Patient and investigator global evaluation of treatment also favoured fentanyl for "troublesome side-effects" and "less interruption of daily activities". The authors concluded that transdermal fentanyl is as effective as, but better tolerated than, sustained-release morphine as first-choice opioid for treatment of cancer pain. Another study compared fentanyl, morphine and methadone in the management of cancer pain (13). All three drugs were found to be similarly effective and well tolerated. There were no differences in pain intensity between the three treatment groups, or in consumption of non-opioid analgesics, at any time point. No relevant differences in quality-of-life scores, symptom intensity or distress scores were observed between treatment groups. Residual fentanyl in used transdermal patches after 72 hours has been reported to be between 28% and 84.4% (14, 15). Potential for harms, misuse and abuse is associated with residual fentanyl in used patches and appropriate, safe disposal is essential.

Rapport coût/efficacité

No information regarding costs or cost–effectiveness was provided in the application. In a cross-sectional study of the global availability and prices of five opioids (morphine, methadone, fentanyl, hydromorphone and oxycodone), oral methadone was found to be the least expensive, with a median price of US$ 0.5 for 30 days of treatment (17). The median price of transdermal fentanyl for 30 days of treatment was US$ 2.2 while that of immediate-release oral morphine tablets/capsules was US$ 18.9.

Directives de l'OMS

The WHO guidelines for management of cancer pain are currently under review. WHO's 2012 guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (16) recommend the use of strong opioid analgesics for the relief of moderate to severe persisting pain in children (strong recommendation, low-quality evidence). Morphine is recommended as the first-line treatment choice. There is insufficient evidence to support recommendation of alternative opioids as first choice. The guidelines go on to recommend switching opioids and/or route of administration in the event of inadequate analgesic effect with intolerable side-effects (strong recommendation, low-quality evidence). Alternative opioids listed in the guidelines are fentanyl, hydromorphone, methadone and oxycodone. Oral administration is recommended.

Disponibilité

Fentanyl, like morphine, is subject to international control under the Single Convention on Narcotic Drugs, 1961.

Autres considérations

WHO is currently developing new cancer pain guidelines, which are due for completion in late 2017 or early 2018.

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon: International Agency for Research on Cancer; 2013 (http://globocan.iarc.fr, accessed 20 March 2017).
2. Fischer DJ, Villines D, Kim YO, Epstein JB, Wilkie DJ. Anxiety, depression, and pain: differences by primary cancer. Support Care Cancer. 2010;18(7):801-10.
3. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol. 2007;18(9):1437–49.
4. Greco MT, Roberto A, Corli O, Deandrea S, Bandieri E, Cavuto S et al. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. J Clin Oncol. 2014;32(36):4149–54.
5. Kornick CA, Santiago-Palma J, Moryl N, Payne R, Obbens EA. Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. Drug Saf. 2003;26(13):951–73.
6. Raptis E, Vadalouca A, Stavropoulou E, Argyra E, Melemeni A, Siafaka I. Pregabalin vs. opioids for the treatment of neuropathic cancer pain: a prospective, head-to-head, randomized, open-label study. Pain Pract. 2014;14(1):32–42.
7. Hadley G, Derry S, Moore RA, Wiffen PJ. Transdermal fentanyl for cancer pain. Cochrane Database Syst Rev. 2013;(10):CD010270.
8. Koyyalagunta D, Bruera E, Solanki DR, Nouri KH, Burton AW, Toro MP et al. A systematic review of randomized trials on the effectiveness of opioids for cancer pain. Pain Physician. 2012;15(3 Suppl):ES39–58.
9. Mystakidou K, Katsouda E, Kouloulias V, Kouvaris J, Tsiatas M, Vlahos L. Comparison of transdermal fentanyl with codeine/paracetamol, in combination with radiotherapy, for the management of metastatic bone pain. J Opioid Manag. 2005;1(4):204–10.
10. Othman AH, Mohamad MF, Sayed HA. Transdermal fentanyl for cancer pain management in opioid-naive pediatric cancer patients. Pain Med. 2016;pii:pnw004.
11. Hemati K, Zadeh PR. The incidence of severe diarrhea with transdermal fentanyl patch: an uncommon event. J Clin Diagn Res. 2015;9(6):UD01–2.
12. van Seventer R, Smit JM, Schipper RM, Wicks MA, Zuurmond WW. Comparison of TTS-fentanyl with sustained-release oral morphine in the treatment of patients not using opioids for mild-to-moderate pain. Curr Med Res Opin. 2003;19(6):457–69.
13. Mercadante S, Porzio G, Ferrera P, Fulfaro F, Aielli F, Verna L et al. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. Eur J Pain. 2008;12(8):1040–6.
14. Marquardt KA, Tharratt RS, Musallam NA. Fentanyl remaining in a transdermal system following three days of continuous use. Ann Pharmacother. 1995;29(10):969–71.
15. Breitbart W, Chandler S, Eagel B, Ellison N, Enck RE, Lefkowitz M et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Oncology (Williston Park). 2000;14(5):695–705; discussion 9–17.
16. WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/44540/1/9789241548120_Guidelines.pdf, accessed 20 March 2017).
17. De Lima L, Pastrana T, Radbruch L, Wenk R. Cross-sectional pilot study to monitor the availability, dispensed prices, and affordability of opioids around the globe. J Pain Symptom Manage. 2014;48(4):649–59.e1.