Pharmacy and Wellness Review

Volume 2 | Issue 1 Article 8

March 2011

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Abstract

Approximately 80 percent of cancer patients experience breakthrough pain (BTP) characterized by acute onset, short duration, and moderate-to-severe intensity. Treatment of BTP using current available medications is often insufficient, leading to the development of various novel approaches that focus on rapid onset of action and short duration of action. Most of these products are still in clinical trials, and future studies are needed to compare the novel approaches to currently available treatments. Non-medication related issues, which arise from a lack of communication and understanding between the patient, physician and pharmacist, are also barriers to adequate BTP management. By educating patients and working with physicians, pharmacists can play a major role in effectively managing cancer-related BTP.

Introduction

Cancer-associated pain is a serious clinical concern for patients and caregivers. It is a common occurrence in many cancer types and can be caused by both the disease and the treatment. It is important for health care professionals and patients to understand that there are two kinds of cancer pain that need to be managed: chronic baseline pain and breakthrough pain (BTP). The World Health Organization states that 90 percent of patients achieve adequate relief of chronic pain from relatively simple drug therapies.[1] Unfortunately, even when this baseline pain is managed effectively, instances of BTP still occur in upwards of 80 percent of patients.[2] The specific clinical features of BTP vary among individuals but are characterized by acute onset, short duration, and moderate-to-severe intensity. A 2008 study showed the median number of BTP episodes per day was two with a range of one to 10, and the median duration of each event was 30 minutes with a range of five seconds to 360 minutes.[2] Because traditional treatment of BTP in cancer patients is complex and often insufficient, various novel approaches are being studied.

Traditional Treatment

BTP is traditionally managed with oral immediate-release (IR) opioids. These are taken as needed in adcition to regularly scheduled analgesics for chronic pain management. However, oral IR opioids are not an ideal choice because of delayed onset (average onset of action is 30-40 minutes) and a longer duration of action than needed for most BTP episodes.[3] When patients believe their rescue medication is taking effect, it may actually be the result of the BTP episode resolving on its own. Patients also may believe that they need to take additional doses of their medication when they do not experience rapid pain relief; in reality, their initial dose most likely has not yet taken effect. An ideal medication for the treatment of BTP would have a more rapid onset of action and shorter duration of action than those currently used.

Novel Approaches

Alternate routes of opioid administration may be able to achieve greater efficacy in managing BTP. Various transbuccal, sublingual and intranasal products can offer better bioavailability, quicker onset of action, and shorter elimination half-lives. While some of these opioids are currently available, others are still in clinical trials.

Transbuccal

Transbuccal administration of medications occurs via the transmucosal route often behind the rear molar, between the upper cheek and gum. Transbuccal medications with a labeled indication for BTP include fentanyl buccal tablets (FBT), oral transmucosal fentanyl citrate (OTFC) lozenges, and fentanyl buccal soluble film (FBSF).[4] These transbuccal dosage forms allow for increased bioavailability in comparison with traditional forms of opioid treatment, with an onset of action five to 15 minutes after administration. A 2007 study by Darwish et al. indicated that FBT resulted in higher early systemic exposure and higher peak concentrations at the same dosage strength as OTFC lozenges (t_{max}= 46.8 min and C_{max}=1.02 ng/mL vs. t_{max}= 90.8 min and C_{max}=0.94 ng/mL, respectively).[5] In addition, Vasisht et al. demonstrated that FBSF achieved greater plasma concentrations in roughly the same amount of time as OTFC lozenges ($p = 0.03$).[6] In a separate study also conducted by Vasisht et al., the bioavailability and transmucosal absorption of fentanyl via both FBSF and FBT were significantly higher when compared to oral administration, i.e. following the buccal doses, mean C_{max} and AUC_{inf} were 1.9 and 2.0 times that of oral administration.[7] While FBSF and FBT have shown quicker time to onset and better efficacy than OTFC, it is important to note that all three dosage forms have been statistically significant in decreasing the frequency and intensity of BTP in comparison to placebo in each of their respective studies.

Sublingual

The development of a sublingual dosage form was intended to potentially exploit a more rapid onset of action compared to other transmucosal opioid formulations. A double-blind, cross-over trial by Lannernas et al. studied the pharmacokinetics of three fentanyl sublingual tablet dosage strengths, 100 µg, 200 µg, and 400 µg.[8] Time to first detectable plasma concentrations (t_{first}) for all doses ranged from eight to 11 minutes and time to peak concentrations (t_{max}) varied from 45-60 minutes with a statistical non-significant increase in t_{max} in correlation to increasing dosage strengths (p=0.19-0.57). A single case study by Kunz et al. utilizing a more potent analogue of fentanyl, sufentanil, was found to provide "satisfactory" analgesia of BTP with 25 µg doses every three minutes (max dose of 75 µg).[9] The rapid onset of action of these sublingual products is promising; however, further studies need to be done in a larger patient population comparing these to traditional treatments and the other novel approaches.

Intranasal

The absorption of morphine, fentanyl, sufentanil or ketamine via the nasal cavity have all been assessed in clinical trials for BTP management. Pavis et al. studied an intranasal morphine-chitosan formulation that was found to have a duration of action of five to 45 minutes and to be effective (receiving a score of 1, or slight pain, on a 0-4 pain scale) in the relief of BTP at doses varying from 5-80 mg.[10] A randomized, double-blind, crossover study of fentanyl pectin nasal spray (FPNS) conducted by Portenoy et al. found the treatment to be "proven safe, well tolerated, and rapidly efficacious," improving mean summed pain intensity difference from 10 min ($P < 0.05$) until 60 min ($P < 0.0001$) in comparison with placebo using a 10-point pain scale.[11] Intranasal sufentanil also has been proven successful in the treatment of BTP. Good et al. reported a significant reduction in pain scores at 15 ($P < 0.0001$) and 30 minutes ($P < 0.0001$) in a prospective, open-label, observational study of 30 patients.[12] Currently entering phase III clinical trials is PMI-150 (intranasal ketamine) for the treatment of BTP in cancer patients. While other studies have assessed ketamine and determined its use sufficient in the treatment of BTP postoperatively, its effect on BTP in cancer patients never has been studied until now.[13] As with the other novel approaches, the intranasal medications show promise, but additional studies need to be performed to provide further support for their use in place of traditional treatments.

Challenges

The primary challenges associated with the use of these novel agents include observable side effects, dose titration of opioid treatment, availability, and cost. While these medications are short-acting, they still share a similar side effect profile of traditional opioids, including nausea, vomiting, constipation, dizziness and/or drowsiness.[1] Additional side effects associated with their respective route of administration have been observed. For example, intranasal irritation has been associated with the intranasal route of administration.[10] Another challenge is titration to a patient-specific effective dose. An effective dose is rarely achieved on the first attempt, as a result of the limited data available for the use of these agents, but is obtainable after a few administrations. With exception of the transbuccal opioids, the novel agents discussed are still in clinical trials and are not available for public use. The transbuccal opioids that are available are costly. Twenty 400 µg generic OTFC lozenges cost $400, and 28 200 µg Fentora® FBTs cost $660 in comparison to a traditional oral cancer pain agent such as 30 5-500 mg hydrocodone/acetaminophen tablets at $12.[4] Until these issues can be resolved, BTP will remain a difficult element of cancer treatment, leaving patients seeking answers from health care providers.

Discussion

Other challenges in the management of BTP are independent of the medications. These arise from a lack of communication and understanding between the patient, physician and pharmacist. Davies et al. found that 48 percent of patients cited an inappropriate reason as a primary or secondary concern for why they were not taking their prescribed breakthrough medication. These reasons include apprehension about adverse effects, the possibility of becoming physically dependent, or the possibility of becoming psychologically dependent.[2] Ensuring that patients truly understand the risks and have adequate opportunity to voice concerns is paramount to effective pain management. Furthermore, some physicians neglect to recognize the effect BTP may have on a patient and may place restrictions on how often an emergency dose can be taken. The same study mentioned above concluded that only 44 percent of patients were told they could take rescue medications as needed, and 15 percent were told they could not take the medications more than three times a day. This led to 80 percent of the patients using non-pharmaceutical methods to manage BTP. These methods included resting, exercising, application of heat, changing position and consumption of alcohol. Pharmacists have the opportunity to play a significant role by taking time to counsel patients about their pain medications and the management of their symptoms. As new and unique treatments become available, it will become even more important for the physician, pharmacist and patient to communicate and work together to develop the best pain management plan for each individual.

As the most accessible health care provider to patients, it is important for pharmacists to understand the reality of BTP and the current treatments available as well as those in development. A pharmacist's ability to identify this phenomenon within community, hospital, and palliative care settings is essential to maximize patient treatment outcome. By recognizing these instances of BTP, patients can be directed to their physicians for optimal treatment. Pharmacists can aid physicians in the accurate direction of BTP treatment by providing information about novel agents. While there is an obvious need for better treatment options for cancer-related BTP, further studies need to be conducted regarding the use of the novel approaches before they will significantly change clinical practice. Studies comparing these products to traditional treatments, rather than placebo or themselves, also will be necessary.

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