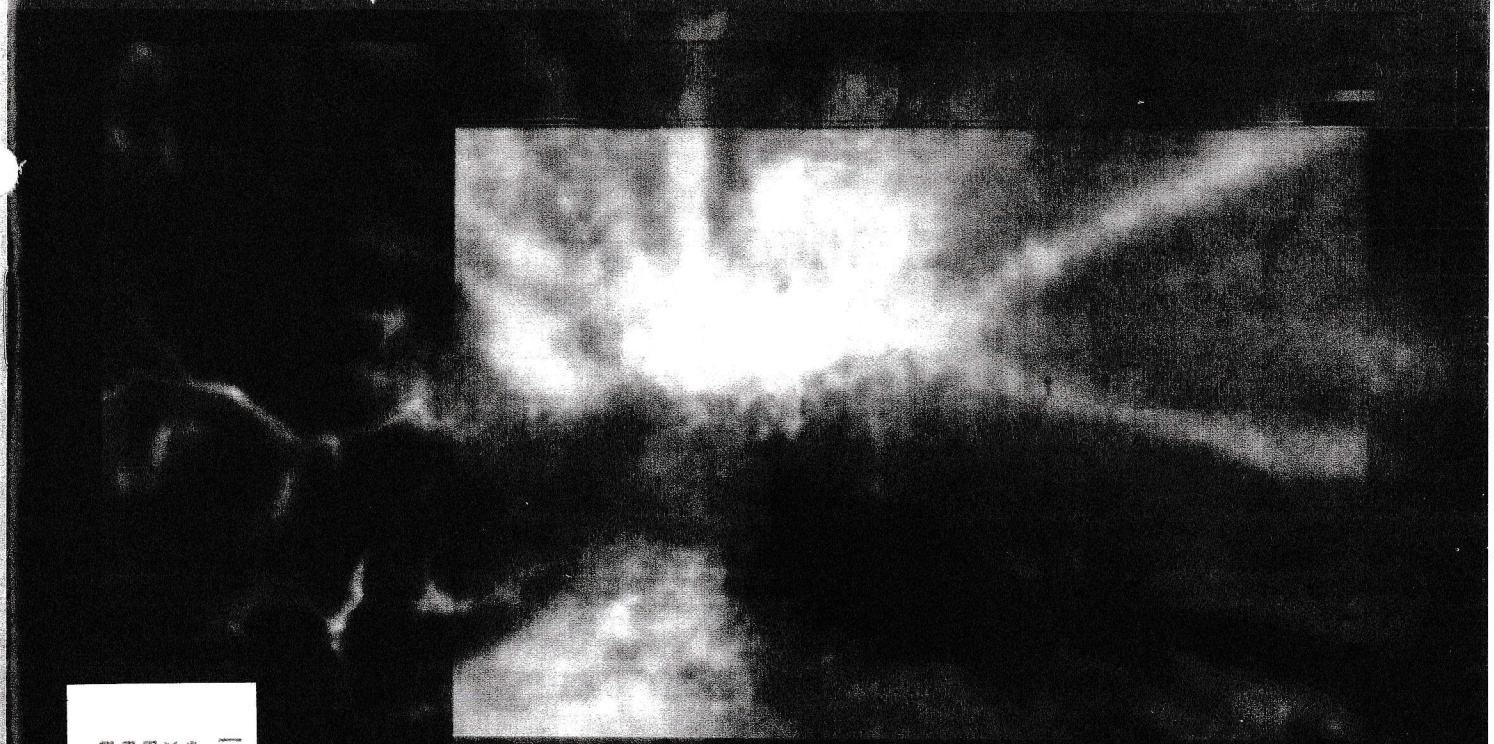
VOLUME 6, NUMBER 1 JANUARY/FEBRUARY 2004



The Pain Clinic

A Multidisciplinary Approach to Acute & Chronic Pain Management

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Oral Transmucosal Fentanyl Citrate in the Outpatient Treatment of Severe Pain From Migraine Headache

Oral Transmucosal Fentanyl Citrate in the Outpatient Treatment of Severe Pain From Migraine Headache

Despite major advances in the treatment of migraine in the past decade, patients frequently fail to respond and require some form of crisis management.

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Migraine encompasses a wide variety of manifestations, confounding decisions that would optimize treatment. When a primary headache disorder is identified, the goal of treatment is to reduce the frequency and severity of attacks as quickly as possible. A new class of medications, the triptans, often answers this need. Triptans have been shown to be effective in 60% to 70% of patients within 2 hours without debilitating side effects; however, 30% to 40% of patients remain unsuccessfully treated.[1] Prophylactic medications, such as beta blockers, calcium channel blockers, and anticonvulsants, reduce the number of headache days per month by an average of 50%. Oral analgesics and antiemetics may rescue migraineurs from intractable pain; however, a large proportion of patients still fail to find relief.[2] Consequently, many patients with uncontrolled migraine headache seek treatment in an emergency department (ED) or urgent care center.

More than 800,000 people per year visit the hospital ED for the treatment of migraine in the United States. Eighty-five percent of these people require parenterally administered agents, including opioid preparations and antiemetics.[3] The ED, however, is not an ideal place for the migraine patient since it is associated with significant cost (often $500 or more) and time. The average time in the ED is 265 minutes and because patients usually require a driver, the time each person spends in the ED should be multiplied by two. Migraineurs often find the ED environment too bright, loud, and odiferous. For all these reasons, an outpatient treatment program for migraine headache would be more effective than the ED for providing relief of pain.[4,5] Migraine headache pain is analogous to breakthrough pain, which is a transitory exacerbation of pain that occurs in persons with a background of stable yet persistent pain.[6] Episodes of breakthrough pain are often characterized by unpredictable and rapid onset of moderate to severe intensity. The ideal management of breakthrough pain, therefore, requires rescue medicines that not only act rapidly but also can be titrated to the individual needs of each patient.

Oral transmucosal fentanyl citrate (OTFC, ACTIQ) is a novel opioid product designed to deliver rapid analgesia to patients who experience breakthrough pain.[7-9] OTFC is available in six dosage strengths ranging from 200 µg to 1600 µg, thus allowing individualization of dosing. The effective dose for each patient is determined by titration.

The onset of meaningful pain relief with OTFC is 5 to 10 minutes and the duration of pain relief is approximately 2½ to 3½ hours.[7]

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with this treatment program and have been universally positive in their assessments. Additional controlled studies in larger patient populations are warranted to evaluate OTFC in the outpatient treatment of migraine-associated headache pain, including time to onset of pain relief and safety considerations.

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Absorption of fentanyl through the oral mucosa is approximately five times faster for OTFC (T_{max} of 23 minutes) than for oral fentanyl (T_{max} of 101 minutes) and the bioavailability is 50%.[10] The relative potency of OTFC has been compared with intravenous (IV) morphine and was found to be approximately 10:1, implying that 200 µg of OTFC is equivalent to 2 mg of IV morphine, or 6 mg of oral morphine (using a 3:1 conversion rate for IV morphine/oral morphine).[7] Thus, using standard conversion values, 200 µg of OTFC is equivalent to 4 mg of oral oxycodone and 1.5 mg of oral hydromorphone.

These were the features, specifically the potency and the rapid onset of pain relief, that first interested us in the use of the OTFC for crisis management in the migraineur. Our initial studies were performed in the office setting for the treatment of acute migraine.[11] The use of OTFC for refractory migraine pain in outpatients was recently reported by Jenson and colleagues[12] and by Landy[13] at the 2003 American Headache Society meeting. OTFC reduced pain intensity and allowed migraineurs to avoid ED visits, most commonly using 400 and 800 µg doses.

We performed a study using OTFC in the treatment of acute breakthrough pain, specifically in outpatient migraine patients who described having severe, uncontrollable pain. All of these patients had pain severe enough to warrant emergency treatment. Also, all of these patients had used OTFC for treatment of a single headache in our office on at least one previous occasion while under careful observation. Eligibility for inclusion in the study required that the first treatment be administered in the office. Since OTFC is approved by the FDA for use only in opioid-tolerant patients, all patients required monitoring for adverse events. We evaluated these patients in an outpatient setting to establish the effectiveness and tolerability of OTFC in their headache disorder treatment plan.

METHODS

A total of 28 patients were enrolled in the study. All of the patients had been under our care for the treatment of chronic and severe headache disorders, specifically severe migraine pain. All of them had been evaluated in our office and had undergone full examinations and neurological or medical evaluations, based on their specific needs. None of them was taking chronic opioid therapy. All patients had previously been treated in our office with OTFC for acute breakthrough migraine pain. After initial treatment in our office setting, each patient was given a prescription for OTFC dosage strengths to match their needs. Patients would start treatment by consuming 400-µg units and would either take another 200 µg if their successful dose was 600 µg or subsequent 400-µg units if their successful dose was 800 µg or 1200 µg. When more than one unit was required they were taken at 25-minute intervals.

Each patient was expected to use medication for managing headache pain at home, reserving the OTFC as a rescue medicine for refractory headache pain only after failure of their usual and customary regimens including triptans, antiemetics, nonsteroidal anti-inflammatory drugs, opioids muscle relaxants, and over-the-counter preparations. Pain was measured on an 11-point numerical scale, 0 = no pain to 10 = worst pain imaginable. Patients were permitted to use OTFC for refractory migraine pain for up to two events per month. They were instructed to record their analgesic response to OTFC and any adverse events on a questionnaire and were required to return all questionnaires to our office for evaluation. Outpatient use of OTFC was monitored up to 1 year.

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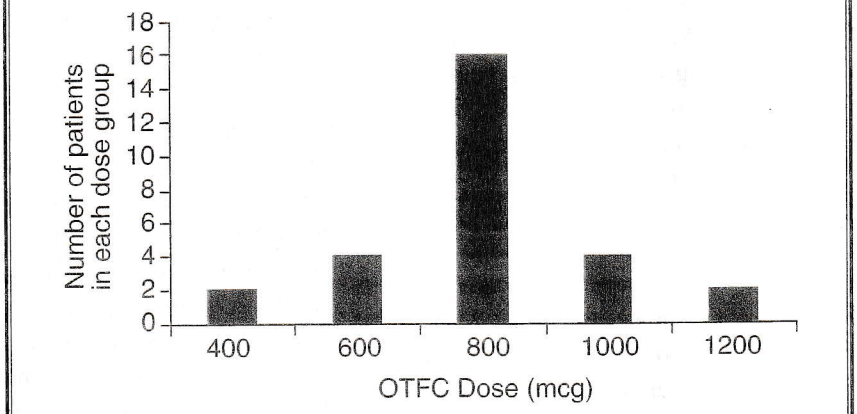
RESULTS

Modal OTFC total dose per episode for achieving effective relief from migraine headache pain was 800 µg. This was usually accomplished by the sequential use of two 400-µg units with a 25-minute period between dosing units. Dosing of OTFC ranged from 400 to 1200 µg (Figure). The mean rate of OTFC usage,as a rescue medicine for recurrent acute refractory migraine headache pain over the 1-year period was 7 (median, 4; range, 1 to 30).

All 28 patients who had used OTFC for treatment of acute refractory migraine headaches at home were able to avoid an ED or urgent care center visit while they were using the treatment. Twenty-seven of the 28 patients (96%) reported that significant relief of pain was achieved during OTFC usage. One patient experienced minimal relief, but still avoided the ED. Thirteen of the

FIGURE OTFC dose providing effective outpatient pain relief (n=28).



28 outpatients (46%) had initially quantified their pain intensity as 7 or greater on the 11-point scale. The mean improvement of pain with OTFC was 7 points reducing the pain from severe to mild. Patients likewise reported corresponding reductions of the International Headache Society features of migraine, including photophobia, phonophobia, and osmophobia.

OTFC was generally well tolerated. Nausea from usage of OTFC was reported by five patients (18%), all of whom routinely experienced nausea during migraine headaches. A few patients complained of itching that was easily relieved by diphenhydramine. Some patients reported somnolence or fatigue, but all remained ambulatory. No patient experienced respiratory alterations of any sort—a concern with the use of OTFC in nonopioid-tolerant patients. Many patients reported that OTFC was much more tolerable than their usual crisis management medications, ie, meperidine.

DISCUSSION

OTFC was effective for the outpatient treatment of acute refractory migraine headache pain when titrated for effectiveness in migraineurs who had used this medication previously in our clinic. The response was consistent with the analgesic effect reported with the use of OTFC in patients with other forms of pain management.[7-9] None of them had been on daily outpatient opioid therapy. We observed no significant difference in the response to OTFC in patients who had taken previous medications, including triptans, antiemetics, nonsteroidal anti-inflammatory drugs, opioids muscle relaxants, and over-the-counter preparations, for their headache. Additive central nervous system effects were not observed in our population since patients titrated their individual OTFC dosage based on the level their pain and their tolerance to the medication. Since the T_{max}, the time to peak concentration of fentanyl, of OTFC is less than 25 minutes, 10 patients can quickly assess their response to the medication.

It has been our continuing impression in more than 500 uses of OTFC for headache pain in nonopioid-tolerant individuals over the past 3 years that the presence of moderate to severe pain—which was the circumstance in the majority of the patients in this study—decreases the incidence of potential respiratory depression with OTFC. Previous studies at the University of Utah have demonstrated respiratory effects including low respiratory rates and oxygen desaturations even in low doses (eg, 400 µg) in opioid-naïve healthy male volunteers participating in an OTFC pharmacokinetic study who were not in pain.[14] We did not find clinical evidence of respiratory depression in our study, which was consistent with findings in opioid tolerant patients with breakthrough cancer pain.[8,9]

Although personal anecdotal data cannot be considered scientific evidence, it has been our observation that OTFC has received the highest rating by migraineurs of any medication, including the triptans, we have ever used for headache in our clinic. It is possible that the ED offers such an unpleasant experience for the migraineur that anything that obviates an ED visit is given highly positive reviews.

CONCLUSIONS

OTFC is an effective outpatient treatment for acute refractory migraine headache pain and could reduce health care use, especially ED visits. Our patients had great success