

Reduction in Medication Errors: The Fentora Case Study

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Abstract

Fentora (fentanyl citrate) is an analgesic opioid used in the management of breakthrough pain in adult cancer patients. Numerous reports of medication errors had been reported since the product's launch in 2006, 74% of which were prescribing errors. Subsequent to the initiation of a risk evaluation and mitigation strategy (REMS) by FDA and the sponsor in 2011, reports of prescribing errors dropped rapidly. It is likely the REMS had a significant impact on the safe use of this important product. While further data from subsequent years would be needed to confirm this hypothesis, this is one of the first reports of an FDA and industry cooperative effort that showed a rapid increase in the safe use of a marketed pharmaceutical product as result of a REMS program.

Keywords

FDA, risk evaluation and mitigation strategy, Fentora, fentanyl, prescribing error

Introduction

Postmarketing surveillance has become a crucial part in the drug development process, as it is very difficult to anticipate all the adverse effects that are likely to be associated with an investigational drug during development. FDA has therefore initiated a system for postmarketing surveillance and risk assessment. The agency takes appropriate actions, which might include withdrawing drugs from market or changing the labeling of the drugs, if the safety profile of a new drug changes.¹

As part of postmarketing surveillance, FDA receives reports on medication errors. These reports are analyzed by the National Coordinating Council for Medication Error Reporting and Prevention, an independent standard-setting body that deals primarily with definitions and taxonomy of medication errors. A medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the healthcare professional, patient, or consumer."² These errors could be associated with the practices of health care professionals or related to procedures such as dispensing, distributing, or administering drugs. Most medication errors occur as a result of misinterpretation of drug orders due to poor handwriting, confusion among drugs with similar names, or confusion of the metrics or dosing of drugs. Medication errors are generally subdivided into prescribing errors, dispensing errors, and administration errors. Drug-prescribing errors are made when an inappropriate drug is selected for a

patient. Lack of proper knowledge about the prescribed drug, patient history, and/or not knowing the recommended dose for a drug are the factors contributing to prescription errors. Dispensing errors arise at any stage, starting from issuance of a prescription through dispensing of the drug by the pharmacist. These errors account for 1% to 24% of the medication errors. Administration errors may occur due to discrepancies between the intended dose and the dose administered to the patient.²

The FDA's Division of Medication Errors Prevention and Analysis has established a medication error prevention program staffed with health care professionals who analyze the adverse events reports sent to Med Watch and provide possible solutions to minimize the risks occurring through these medication errors.³

FDA has undertaken the following measures to minimize medications errors:

- FDA reviews more than 300 drug names a month to avoid confusion among the drug names and to minimize the medication errors that arise due to similarity in names of the drugs.⁴

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- FDA ensures that all drugs are labeled according to regulations to minimize medication errors caused by the health care professionals.
- FDA works with drug companies to ensure that their product designs are appropriate.
- FDA ensures that every drug or biologics product has a computerized bar code so that patients receive the correct drug and dose.
- FDA reviews approximately 1400 reports on medication errors annually to identify the causes, and it tries to prevent such types of medication errors from occurring in the future.⁴

Fentora

Fentora (fentanyl citrate; Cephalon, Franzer, PA, USA) is one of many marketed drugs that may lead to medication errors when used improperly. Fentora was chosen as the case study to investigate the effectiveness of measures taken to minimize medication errors.

There are many drugs used in the management of breakthrough pain in cancer. However, Fentora, an analgesic opioid, is the most potent among all the drugs used. Fentora is used in the management of breakthrough pain in adult cancer patients.⁵ It is a prescription drug that contains fentanyl citrate as the active ingredient, and it is available in tablet form in doses of 100, 200, 400, 600, and 800 mcg. It is very important that Fentora be prescribed for patients who are opioid tolerant, as it may cause serious adverse events or even death if used by non-opioid tolerant patients.⁶ The route of administration is through the buccal cavity; it is designed to be placed in the buccal cavity to allow maximum drug disintegration.⁷ Modern OraVescent technology is used in the drug delivery system to enhance the absorption in the oral cavity. Fentora was approved by FDA on September 25, 2006.⁷

Medication errors with the use of Fentora have been associated with the following⁸:

- Lack of knowledge among physicians about the drug labeling—the product has been prescribed to patients who are not opioid tolerant.
- Pharmacists mistakenly dispense Fentora as a substitute for other fentanyl products.
- Pharmacists dispense different doses of fentanyl products instead of Fentora.
- Physicians and pharmacists are not aware of either the misuse or the abuse potential of Fentora.

Given the potentially serious consequences of medication errors with Fentora yet also the clear importance that this drug

has in the clinician's treatment of severe pain, an analysis of reports of medication errors was examined in terms of the success of FDA's actions to minimize these errors.

Methods

Reports of medication errors associated with Fentora between 2006 and 2013 were obtained through a freedom of information request. All reports from October 1, 2006, to February 2, 2013 were analyzed. Medication error analysis was limited to reports from within the United States. The reports were sorted by type of error, and their occurrences were examined in relation to FDA safety alerts, labeling changes, and the risk evaluation and mitigation strategy (REMS) for Fentora. A regression analysis was done on the lines generated by the number of each type of medication error reported by month from 2006 to 2012.

Labeling changes for Fentora were obtained from the FDA website Drugs@FDA (<http://www.accessdata.fda.gov/Scripts/cder/drugsatfda/index.cfm>), under "Information on Safety Alerts."⁹ The REMS was also obtained from the FDA site.^{9,10}

Results

Fentora was approved on September 25, 2006.¹¹ Fentora was initially approved by FDA with a risk minimization action plan, the goals of which were to avoid the use of Fentora by nonopioid users and to minimize drug abuse and misuse.¹² The manufacturer was to educate the physician, pharmacists, and patients about the risks and benefits associated with the drug; it was to implement a standard plan to avoid the use of Fentora by nonopioid users and to minimize the drug's abuse and misuse.¹²

A safety alert issued on September 13, 2007, stated that health care professionals should strictly abide by the labeling information in the approved labeling and not prescribe Fentora for minor pains, such as headache or regular pain.¹³ FDA issued another safety alert in January 2008 stating that Fentora might cause death and injuries.¹⁴ Cephalon issued a "Dear Healthcare Professional" letter to physicians and pharmacists on September 10, 2007.¹⁵ The letter explained usage, indication, and proper dosing; warned against substitution of Fentora with other fentanyl products; and emphasized proper patient selection, dosing, and administration. FDA also updated the "Indications and Usage" and "Warning and Precautions" sections of the labeling for Fentora in 2011.¹⁶

FDA approved a REMS for the class of transmucosal immediate-release fentanyl (TIRF) products on December 28, 2011.¹⁷ This was the FDA's first REMS approved for opioid drugs. The TIRF REMS program has been in effect since March 2012. The TIRF REMS attempted to minimize the misuse, abuse, and overdosing of the drugs.¹⁸ The TIRF REMS program required the enrollment of physicians, pharmacists,

Table 1. FDA's labeling revisions on Fentora.

Date of Change	Labeling Changes
April 27, 2007	Boxed warning updated; concomitant use of Fentora may cause fatal respiratory depression. ¹⁸
February 7, 2008	The revised items include labeling, medication guide, and carton containing label to enhance the safety information. ¹⁹
December 2, 2009	Suicidal tendency added and updated the dosage to avoid the side effects associated with overdose of Fentora. ²⁰
December 28, 2011	Risk evaluation and mitigation strategy for the class of transmucosal immediate-release fentanyl prescription medicines. ¹⁷
June 5, 2012	Updated the boxed warning with warning of respiratory depression, medications errors, and abuse potential. ²¹

and inpatient and outpatient pharmacies to prescribe or dispense the drug. The TIRF REMS also required patients to be informed of the risks associated with using Fentora products. Patients were required to register for the TIRF REMS program.¹⁸

The TIRF REMS access program required

- physicians and pharmacists dispensing the drug to make sure that it is prescribed and dispensed only to the eligible patients who are already on round-the-clock opioid therapy;
- health care providers to avoid the substitution of Fentora for other fentanyl products and vice versa;
- health care providers to prevent the sharing of the fentanyl products among patients who are not eligible to receive the drug and/or not prescribed it;
- health care providers to be made aware of and educated about the misuse, abuse, and overdosing of the drug; and
- that Fentora be available only through the TIRF REMS program to patients who are enrolled in it and eligible to take the drug.

A summary of the labeling changes for Fentora is provided in Table 1.

The FOI report for medication errors reported on Fentora was dated April 23, 2013. All reports from 2006 to 2013 were evaluated and sorted by type—that is, prescription errors, dispensing errors, or administration errors (Figure 1). Prescription errors occur when a patient does not receive the recommended dose due to instructions of a physician. Dispensing errors occur because of improper dispensing of drugs by a pharmacist. Administration errors occur due to the improper route of administration of the drug.

Based on the data in Figure 1, changes in the 3 types of medication errors were analyzed. Only administration errors show a statistically significant regression line over time ($P < .05$), and this was an increase. These errors, however, were only a fraction (6%) of the 330 reports of medication errors received through February 2013. In fact, 243 (74%) were reports of prescribing errors. Another 61 (18%) were coded simply as medication errors and not further differentiated. For the 6 full years of marketing reports available,

these prescribing error reports peaked in the third year (2009) and then seemed to decrease through year 6 (2012).

Discussion

It seems very likely that the bulk of the medication errors and subsequent patient injuries due to Fentora were related to incorrect prescriptions written by physicians. Given that 74% of the total medication errors reports may be classified as prescribing errors, the area of concern seems to be physician rather than pharmacy or nursing errors. The consistent increases in these errors in the first 3 years of marketing are likely related to an increase in use and market penetration by Fentora. Most interesting, however, is the leveling off of reports shortly thereafter and then the rapid fall from a peak of 73 reports in year 3 to 6 reports in year 6. Another 18% of the reports were listed only as medication errors and not further differentiated. These reports followed a pattern similar to that of prescription errors; thus, the true percentage of medication error reports due to prescribing errors may be higher than the stated 74%.

A number of factors may have affected the decrease in reports of prescribing error. First, physicians may have simply learned how to better use the new formulation, thus decreasing their propensity for error. Second, reporting itself may have decreased and actual errors not decreased. After a drug has been on the market for years, the urgency to report adverse events or errors may seem less important to busy health care professionals. Third, the prescription rate for Fentora may have decreased and the actual error rate not changed. Finally, FDA and manufacturer efforts to curb errors may have reduced the real number of errors that occurred.

The FDA-mandated REMS for Fentora that was instituted at the end of 2011 may have had a significant impact on the error rate. Given the restriction to physicians who had to be enrolled in the REMS program, it is likely that these physicians, who were now trained and familiar with the correct use of Fentora, made far fewer mistakes than would a general population of physicians before the REMS introduction. It does appear that the number of prescribing error reports had begun to decline before the formal institution of the REMS, but this may be related to publicity and activities of the

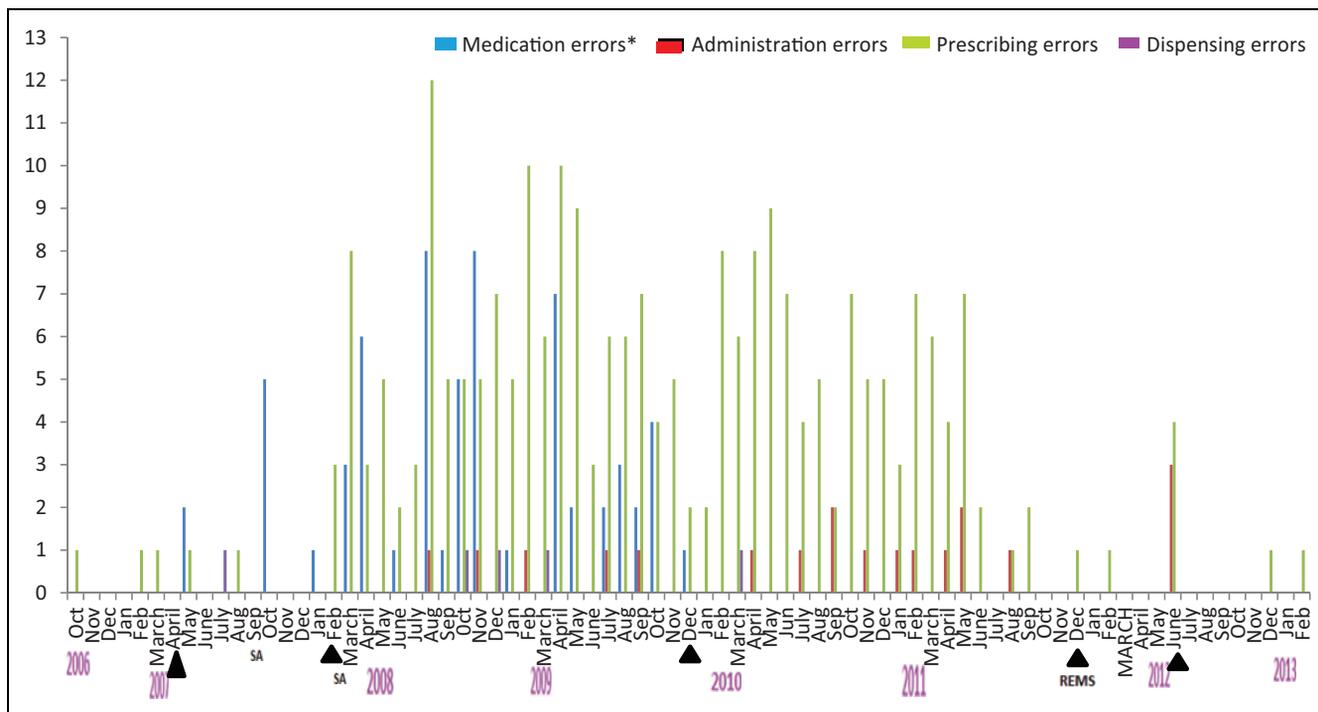


Figure I. Types of medication errors cases of Fentora by month. Months marked with a solid triangle were the months of labeling changes. SA, safety alert issued; REMS, month of Fentora risk evaluation and mitigation strategy approval. *Medication errors are those not further differentiated by type in FDA reports.

Fentora sales force before the finalization of the REMS. Occasional reports were seen after the REMS was instituted, but note the virtual elimination in reports of prescribing errors after the labeling change of June 2012.

Other types of medication errors, specifically dispensing errors, were reported at such a low rate that the impact of FDA actions is difficult to see. Reports of these relatively rare events did not seem to correspond to labeling changes or the REMS institution.

The addition of the number of prescriptions written or units dispensed per year would further elucidate the relationship between reports of medication errors and FDA actions, but these data were not available to the authors. While further data from subsequent years would be needed to confirm this hypothesis, it seems likely that this report is one of the first of an FDA and industry cooperative effort that showed a rapid increase in the safe use of a marketed pharmaceutical product as result of a REMS program.

Conclusions

Fentora is a highly effective yet risky drug if used incorrectly. Numerous reports of medication errors had been reported since the product’s launch, the majority of which were prescribing errors. Activities by FDA and the sponsor leading to a REMS were followed by a falloff of reports of these prescribing errors.

It is likely that these actions, culminating in the REMS, had a significant impact on the safe use of this important product.

Declaration of Conflicting Interests

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