Brief Quality Improvement Report

A Single Institution's Effort to Translate Codeine Knowledge Into Specific Clinical Practice

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Abstract

Background. Codeine is an unpredictable analgesic because of its variable pharmacokinetic, pharmacodynamic, and pharmacogenetic properties. This variability may lead to ineffective analgesia in some and respiratory depression in others. Despite this, codeine is still widely used. At a pediatric tertiary medical institution, codeine was prescribed despite efforts to inform prescribers of the potentially unpredictable analgesia and serious side effects.

Measures. A retrospective/prospective metric was introduced to determine the frequency of codeine orders as compared with similar institutions using Pediatric Health Information Systems data.

Intervention. Interventions included formal and informal education to prescribers, and replacing codeine with oxycodone for patients aged older than six months and an age-appropriate medication for those patients younger than six months within ordersets. Identifying and addressing the major barriers to change also was a key part of the process.

Outcomes. Codeine use was reduced by 97% from the first quarter of 2008 through the third quarter of 2012. This was accomplished through orderset changes and education. Codeine was completely eliminated from the hospital formulary in January 2013.

Conclusions/Lessons Learned. This quality improvement initiative was successful in eliminating codeine from the hospital formulary. Although education decreased codeine orders, understanding and addressing the barriers to change and directly changing the ordersets were the most effective and efficient for knowledge translation. J Pain Symptom Manage 2014;48:119–126.

Key Words

Quality improvement, pain, pediatrics, codeine, adverse effects, CYP 2D6, analgesics, opioid

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Background

Unfortunately, the translation of research findings to clinical practice is often slow. Although research findings are available, they do not always or readily get translated into clinical practice. Some of the reasons for this include: the lack of access to research and/or refusal to abandon outdated medical knowledge, lack of time to keep up with new research because of the sheer amount of research that is produced, and the inability to understand and translate the research. This is especially true in pain management because analgesics are often prescribed by a wide range of practitioners who may neither specialize in pain management nor be familiar with new developments in analgesic research. This article is an example of how electronic prescribing systems can be used to inform busy clinicians of the developing pharmacological knowledge that can affect prescribing habits and improve patient safety.

Codeine or 3-methylmorphine has been used for many decades for the management of mild-to-moderate pain. There is mounting evidence that codeine has both unpredictable efficacy and safety concerns.[1,2] Codeine itself has little-to-no analgesic properties. It is a prodrug of morphine; therefore, the analgesic effect from codeine is predominantly reliant on the metabolism to active morphine. Codeine is metabolized via three major routes, namely glucuronidation to codeine-6-glucuronide (inactive), *N*-demethylation via the CYP3A4 enzyme to norcodeine (inactive), and *O*-demethylation via the CYP2D6 enzyme to morphine (active).

The CYP2D6 enzyme responsible for the conversion of codeine to its active metabolite morphine is significantly affected by genetic polymorphism. The following breakdown of CYP2D6 metabolizers into four groups is a simplified way to look at a complex enzyme with many genetic variants. Individuals known as extensive metabolizers are those who display typical enzymatic activity and metabolize a predictable amount of codeine into active morphine. They represent the largest portion of the population. Those who carry two inactive alleles are known as poor metabolizers and do not form metabolites dependent on CYP2D6. The poor metabolizer, with the lack of 2D6 activity, produce no morphine from codeine and, therefore, little-to-no analgesic effect. Individuals who have a duplication of the CYP2D6 gene are known as ultrarapid metabolizers and they display excessive metabolism. This group metabolizes a higher than predicted percentage of codeine into morphine. Therefore, these individuals are at an increased risk for the serious side effects of opioids, such as respiratory depression and, in severe cases, death.[2–5] The final class of individuals is known as the intermediate metabolizers. This group does have some 2D6 enzyme activity, but less than the extensive metabolizers. These patients will get unpredictable analgesia and possibly no morphine from codeine. In one study, 36% of the patients had undetectable morphine levels after receiving codeine.[6] The varying 2D6 activity throughout the population results in significant unpredictability in the analgesic effects of codeine. These genetic variations of codeine metabolism in the general population pose serious concerns to the use of codeine. Pretreatment genetic testing can identify the various polymorphisms; however, it is a costly test and not widely available.

The variability of codeine is further complicated by the susceptibility of CYP2D6 and CYP3A4 to drug interactions. It has been estimated that approximately 50% of medications are metabolized by the CYP3A4 enzyme. The CYP2D6 enzyme is also responsible for approximately 25% of the metabolism of medications. There is an extensive list of medications that are considered CYP3A4 inhibitors.[7] Because CYP3A4 is one of the major metabolic pathways for codeine, inhibiting it can lead to an increase in CYP2D6 enzymatic activity and, therefore, the potential for higher morphine levels and increased adverse effects. Alternatively, inhibiting CYP2D6 could decrease the percentage of codeine metabolized to morphine, thus decreasing pain control.

A patient later found to be an ultrarapid metabolizer of CYP2D6 had life-threatening respiratory failure while taking a relatively small dose of codeine (25 mg) three times a day for cough. The patient also was taking clarithromycin and voriconazole (both CYP3A4 inhibitors) concomitantly. The higher percentage of codeine channeling through the CYP2D6 pathway resulted in a toxic level of morphine. The patient