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Selected Topics: Toxicology

COMPARISON OF UNINTENTIONAL EXPOSURES TO CODEINE AND HYDROCODONE REPORTED TO TEXAS POISON CENTERS

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☐ **Abstract—Background: Hydrocodone has recently been reclassified as a Schedule II drug by the United States Drug Enforcement Administration and Food and Drug Administration in order to curtail prescription drug abuse. There is concern that analgesic substitutes, such as codeine, will not be as safe or effective. Objective: The purpose of this study is to compare the demographics, adverse events, and medical outcomes of patients who had unintentional hydrocodone or codeine exposures through the use of a state's poison center database. Methods: The Texas Poison Center Network's database was utilized to find all reported unintentional ingestions or adverse reactions of products containing codeine or hydrocodone. Comparisons were made between the two medications by calculating the rate ratios (RR) and 95% confidence intervals (CI). Results: Children aged 5 years or younger were more exposed to codeine (51.6%). Hydrocodone exposures had more serious outcomes (11% vs. 9%; RR = 0.82; 95% CI 0.73–0.91) and had more nausea (7.1% vs. 2.8%; RR = 0.4; 95% CI 0.32–0.48) and vomiting (6.5% vs. 3.3%; RR = 0.51; 95% CI 0.43–0.62). Hydrocodone had a higher rate of intravenous fluids administration (2.4% vs. 1.7%; RR = 0.71; 95% CI 0.54–0.92) and antiemetics (0.4% vs. 0.1%; RR = 0.23; 95% CI 0.08–0.64). Codeine was more closely associated with dermal reactions and patients were given antihistamines (2.5% vs. 1.3%; RR = 1.88; 95% CI 1.46–2.41) more frequently. Cardiovascular side effects, ataxia, and headache occurred equally between the groups. Conclusions: Both drugs had a wide array of reported side effects, but the overall incidence of serious outcomes was low.** © **2016 Elsevier Inc.**

☐ **Keywords—hydrocodone; codeine; adverse events; Schedule II drugs**

INTRODUCTION

Hydrocodone is a commonly used narcotic analgesic that is associated with abuse (1–4). In the past, combination hydrocodone products have been classified as Schedule III controlled substances (5,6). However, on August 22, 2014, the United States (US) Drug Enforcement Administration (DEA) ruled that hydrocodone combination products are being changed from Schedule III to Schedule II to limit hydrocodone abuse through increased regulation (3,4). This rule went into effect on October 6, 2014. This rescheduling may result in providers and patients seeking alternative analgesics (7,8). However, many of the alternative agents have limitations. Acetaminophen is associated with liver toxicity and the US Food and Drug Administration (FDA) is targeting decreased use of this agent (9–11). Nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with gastrointestinal adverse events and renal injury (12). Tramadol is associated with adverse events related to its effects on monoamine neurotransmitters and its opioid agonism (13,14).

Codeine is an opioid agent with typical opioid-related adverse events. Codeine itself is a very weak opioid receptor agonist. It is considered primarily to be a prodrug that, in order to be active, must be metabolized to

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morphine (15). It is metabolized by cytochrome P450 enzyme 2D6, an enzyme that has many polymorphisms that result in great variations in its metabolism (9,16,17). This has resulted in some patients obtaining too little analgesia, while other patients have become opioid intoxicated (9,18). It is recommended that this agent have limited use in children and it has been removed from the World Health Organization's analgesic ladder in the most recent guidelines (19). The FDA has also issued a black box warning against codeine use in pediatric patients who have undergone tonsillectomy and adenoidectomy for obstructive sleep apnea (20,21). In June 2013, the Canadian Ministry of Health, as well as the European Medicines Agency, restricted codeine to patients older than 12 years in age (20). In March 2015, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee also recommended restrictions on the use of codeine containing medications for cough and cold in children because of the risk for side effects (22).

When the DEA rule for hydrocodone as a Schedule II agent went into effect, it was considered that providers might write more prescriptions for codeine. Because codeine combination products remain as Schedule III, providers may look at the abuse potential as being lower than with hydrocodone and shift toward using more codeine products. The relative safety of hydrocodone vs. codeine should be understood by medical providers as they consider these alternative analgesics. The purpose of this study is to compare the demographics, adverse events, and medical outcomes of patients who had unintentional hydrocodone or codeine exposures through the use of a state's poison center database.

METHODS

The Texas Poison Center Network (TPCN) consists of six poison centers that together service the entire state's population of >25 million people. These poison centers use a common electronic database to collect information on all received calls in a consistent manner. The data fields and allowable data options are standardized by the American Association of Poison Control Centers (AAPCC) (23,24).

For this retrospective study, the TPCN database was searched for all codeine and hydrocodone exposures reported during 2000–2013. Exposures to products containing both hydrocodone and ibuprofen (n = 776) were excluded, as NSAIDs are known to have potential for gastrointestinal side effects and could confound the study results. Exposures with products containing acetaminophen were included, as codeine and hydrocodone are commonly prescribed as a combination product. The potential circumstances, or reasons, for the exposure to an agent are broad; thus, poison centers obtain these data only in broad categories. Only exposures where the circumstances for the contact were "unintentional" or "adverse reaction" were included. Exposures that were intentional (eg, suspected attempted suicide and abuse) or due to malicious intent were excluded. In the first part of this investigation, the distribution of codeine and hydrocodone exposures was determined for year, patient age and gender, particular circumstances of (reason for) the exposure, and presence of additional products/substances. Exposures involving other products/substances in addition to the ones containing codeine or hydrocodone were initially included to more clearly define the total number of unintentional exposures during this time period. Exposures not followed to a final medical outcome were also included in the investigation. Calls from outside of the state were excluded.

In the second part of the investigation, the analyses of medical outcome, management site, adverse clinical effects, and treatments were limited to only those exposures involving a single product containing codeine or hydrocodone, i.e., exposures involving multiple products/substances in addition to the ones containing codeine or hydrocodone were excluded. This was done because the additional product/substance might affect the adverse events, medical outcomes, or management of the exposure.

Descriptions of the groupings within the variables are outlined in the AAPCC National Poison Data System reference manual (24). The circumstances of (reason for) the exposure are based on the intent of the exposure. Unintentional exposures result from unforeseen or unplanned events. Unintentional, general exposures are unintended exposures not otherwise specified, e.g., a child swallowed someone else's medication or an adult accidently took the wrong medication. Unintentional, misuse exposures are unintentional improper or incorrect use of a substance, usually referring to chemicals and not medications. However, exposures are at times miscoded as such. Therapeutic errors are unintentional deviations from a proper therapeutic regimen; for example, a patient took two tablets instead of one tablet. Adverse reactions involve unwanted effects reported by a patient with normal, prescribed, labeled, or recommended use of the product.

The medical outcome or severity of an exposure is assigned by the poison center staff and is based on the observed or anticipated adverse clinical effects. Medical outcome is classified according to the following criteria: no effect (no symptoms due to exposure), minor effect (some minimally troublesome symptoms), moderate effect (more pronounced, prolonged symptoms), major effect (symptoms that are life-threatening or cause significant disability or disfigurement), and death. A portion of exposures are not followed to a final medical outcome due to the poison center staff assessment of