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REVIEW

Extended-release hydrocodone – gift or curse?

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Abstract: Hydrocodone is a semisynthetic opioid, which has been used for decades as a short-acting analgesic combined with acetaminophen (or less commonly ibuprofen). Several long-acting, non-acetaminophen-containing hydrocodone formulations are undergoing trials in the US under the auspices of the US Food and Drug Administration, and may be available shortly. This article reviews some of the advantages (including drug familiarity and lack of acetaminophen toxicity) and potential disadvantages (including altered use patterns and high morphine equivalent dosing) of such a medication formulation. We also discuss the abuse potential of long-acting versus short-acting opioids in general and hydrocodone specifically, as well as the metabolism of hydrocodone.

Keywords: hydrocodone, long-acting opioids, opioid abuse, acetaminophen toxicity, tamper-resistant opioids

Current role of hydrocodone

Hydrocodone, especially prescribed in combination with acetaminophen, is the most commonly prescribed opioid in the US.[1] It is marketed in the US under a wide variety of names, depending upon the amount of acetaminophen present. As an example, Lortab® (UCB Pharma, Brussels, Belgium) has 500 mg of acetaminophen per tablet, Lorcet® (UAD Laboratories, St Louis, MO) has 650 mg, Vicodin® (Abbott Laboratories, Abbott Park, IL) has 750 mg, while Zydone® has 400 mg (Endo Pharmaceuticals Inc, Chadds Ford, PA) and Norco® (Watson Pharma, Corona, CA) has only 325 mg. In tablet form, with acetaminophen, hydrocodone is available in 2.5, 5, 7.5 and 10 mg tablets. Vicoprophen® (Halo Pharmaceutical Inc, Whippany, NJ, for Abbott Laboratories) has 7.5 mg hydrocodone with 200 mg of ibuprofen per tablet. Each of these products has a dosing interval of 4–6 hours, with the number of tablets per day limited primarily by the acetaminophen dose. Currently, the recommended dose for chronic acetaminophen use is 3000 mg/day,[2] which corresponds to 4–9 tablets per day of mixed hydrocodone/acetaminophen products, depending on the formulation. Acetaminophen is the most common cause of acute liver failure in the US, accounting for nearly half of the cases.[3] Because of concerns regarding the recent rise in hepatic toxicity seen with acetaminophen-containing medications, in January 2011 the US Food and Drug Administration (FDA) mandated that combination products should contain no more that 325 mg of acetaminophen per tablet by 2014.[4]

The Drug Enforcement Agency classifies hydrocodone, in combination with acetaminophen or ibuprofen, as a Schedule III drug, because the adjuvant analgesic

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medication (the acetaminophen) supposedly precludes excessive usage. As a Schedule III medication, it can be called into the pharmacy, and up to six refills given. Unfortunately, this can lead to easy over-prescribing, and has the potential for abuse among chronic pain patients. It is concerning that a US government study identified significant numbers of middle school-aged and high school-aged teenagers in the US as having abused hydrocodone with acetaminophen, presumably because of its easy availability.[5] A study of emergency department visits in the US from 2004 to 2008 showed that hydrocodone, along with oxycodone and methadone, caused the highest number of emergency department visits among the opioids.[6] However, an estimate of the abuse risk of hydrocodone adjusted for the volume of prescribing suggested that hydrocodone has one of the lowest rates of abuse for its volume of prescribing.[7]

Medications containing only hydrocodone are rare and are not primarily used as analgesics, but rather are considered to be antitussives. This began to change in 2012, when the US Congress passed an FDA reform bill, instructing the Drug Enforcement Agency to reclassify all products containing hydrocodone from Schedule III to Schedule II.[8] The Senate version of the bill did not contain these instructions, and the final bill signed into law simply instructs the Drug Enforcement Agency to hold hearings on the matter. The intention of Congress appears to be related to combating prescription opioid abuse; however, multiple medical and pharmacy groups have come out against this proposed rule change, as evidenced by the multiple open letters sent to the members of both Houses.

Long-acting opioids

There have been only a few studies that have compared the different long-acting opioids. Key measures that were identified and compared in different trials of one or more long-acting opioids included reduction of pain, improved functional outcomes, pattern suggesting superiority of one agent over another, and rate of adverse events, as well as any subpopulation of patients in which long-acting opioids are more effective (race, age, gender, or type of pain). Eight trials found no statistical difference in pain relief or function between long-acting opioids. In general, there was insufficient evidence to prove that different long-acting opioids are associated with different efficacy or different adverse event rates. Only one poor quality trial directly compared different long-acting opioids, ie, transdermal fentanyl versus long-acting morphine, and gave inconclusive results. Studies that provided indirect data were too heterogeneous in terms of study design, patient populations, interventions, outcomes assessed, and results to make accurate judgments regarding comparative efficacy and adverse event rates. In addition, evidence was insufficient to determine if long-acting opioids as a class are more effective or associated with less harm than short-acting opioids.[9]

A recent review of the scientific literature concerning long-acting opioids concluded that the evidence did not show significant differences between currently available long-acting opioids, and the results were insufficient to draw any conclusions about the relative role of long-acting versus short-acting opioid analgesics.[4] A more limited study by Manchikanti et al comparing patients with chronic pain on short-acting hydrocodone preparations versus long-acting methadone found no difference in compliance or rates of abuse, as assessed by urine drug toxicology.[10] It is interesting to note that in the study of abuse risk of different opioids cited earlier, when adjusted for volume of prescriptions, immediate-release oxycodone had one of the lowest abuse risks, and extended-release oxycodone had one of the highest.[7]

Proposed forms of long-acting hydrocodone

A long-acting formulation of hydrocodone and acetaminophen, Vicodin CR (Abbott Laboratories, Abbott Park, IL), was studied in 2006 to 2008 but was not approved by the FDA. Currently, four pharmaceutical firms are developing long-acting formulations of hydrocodone. Of these, Zogenix Inc (San Diego, CA) completed Phase III trials on Zohydro ER™ and submitted a New Drug Consideration in May 2012. Zohydro ER is an extended-release formulation of pure hydrocodone that uses patented Spheroidal Oral Drug Absorption System (SODAS®) technology.

The SODAS technology is achieved by the extended-release beads that are prepared using sugar and starch spheres, upon which a drug excipient layer is coated, followed by an ammonio-methacrylate copolymer coating. After rapid dissolution of the hard gelatin capsule shell, the permeability of the ammonio-methacrylate copolymer coating allows gastrointestinal fluid to enter the beads and solubilize the drug. After dissolving, the active medication may then diffuse out of the beads at a predetermined rate. This entire process prolongs the in vivo dissolution of the drug and extends its absorption into the body. This allows for both immediate-release and time-release of hydrocodone for twice daily dosing.[11] The SODAS technology is not-tamper resistant. The dose strengths studied range from 10 mg to

50 mg tablets. Phase III efficacy and safety studies have been completed. A 12-month follow-up safety study has also been completed.

Teva Pharmaceuticals (North Wales, PA) has also announced a long-acting hydrocodone tablet given twice daily called TD hydrocodone, which is currently undergoing trials; the "TD" in the name refers to "tamper deterrent", according to the company.[12] Anticipated dosing ranges from 15 mg to 45 mg per tablet. Phase III safety and efficacy studies have been completed[13] and a 12-month follow-up safety trial is ongoing. According to the company, a study of the abuse potential of the 45 mg strength tablet, crushed or intact, has also been completed.[13]

Purdue Pharma LP (Stamford, CT), the manufacturers of OxyContin®, and Egalet (Malvern, PA), are also developing long-acting hydrocodone products. The Purdue Pharma product is being targeted as a once-daily formulation. The Egalet product would feature a tablet that is "impossible" to crush, chew, or dissolve.[14] All such pure forms of long-acting hydrocodone will be Class II drugs and will require risk evaluation and mitigation strategy training for prescribers and dispensers.

In reviewing the literature for temper-resistant solutions, there are only patented products that are not available for clinical use at this time. A prodrug form of hydrocodone has been suggested by forming covalent bonds between the drug and different chemical moieties such as amino acids, peptides, and carbohydrates. When compared with hydrocodone itself, the various prodrug compounds are formulated to produce lower bioavailability if injected or snorted. At higher doses, saturation of the biological conversion process is believed to occur, preventing the "rush" abusers seek from opioids like hydrocodone.[15] Unfortunately, none of these options are being utilized in the proposed products, although there is no evidence that any of the proposed deterrents actually prevent abuse.

Positive aspects of long-acting hydrocodone

Hydrocodone is a well established semisynthetic opioid, which has been used for acute and chronic pain for decades. The availability of long-acting, higher-dose hydrocodone formulations would be expected to provide an additional option for patients who cannot tolerate morphine or oxycodone, and another option for opioid rotation strategies.

A long-acting formulation containing hydrocodone without added acetaminophen would reduce the risk of liver damage that has been observed in patients taking prolonged high doses of analgesics containing acetaminophen. While the evidence is scanty, many pain providers hold that long-acting, regularly scheduled opioids are more effective and less prone to abuse than short-acting opioids for chronic pain. For patients who are prone to chronic headaches or central sensitization conditions such as fibromyalgia, less frequent dosing may reduce the risk of rebound, which theoretically could lead to worsening of such conditions.[16]

Estimations of abuse potential of long-acting hydrocodone

Trials of intravenous opioid administration in opioid abusers have estimated roughly equivalent abuse potential between morphine, oxycodone, and hydrocodone.[17] A similar study found the abuse potentials of oral oxycodone, hydrocodone, and hydromorphone to be similar, despite the lower estimated potency of hydrocodone.[18] Previous medical experience with immediate-release oxycodone and long-acting formulations such as OxyContin suggest that long-acting formulations of potent opioids may be perceived and used very differently than their short-acting counterparts. OxyContin was reported to be widely used by drug abusers, who would crush or dissolve the tablets to release the oxycodone all at once; the medication was reformulated in 2010 to resist this form of tampering. Abuse behavior is not unique to OxyContin but indeed dates back to the beginning of the 20th century, and has been a consistent response to the availability of potent opioids.[19]

Hydrocodone pharmacokinetics, dosing, and potential long-term adverse effects

Time-based administration of chronic opioid therapy has been shown, in at least one study, to result in increased overall opioid dosages and also in higher rates of patient concern about control over their opioid consumption.[20] The higher-end dosage of extended-release hydrocodone, expected to be 45 mg or 50 mg per day, would result in a morphine equivalent of 90 mg or 100 mg per day, which is the level that has been found to be associated with a jump in opioid-related morbidity and mortality.[21] The daily dosage would go significantly higher if prescribers write for patients to take more than one tablet at a time, or to take long-acting hydrocodone more frequently than every 12 hours, as has been commonly done with long-acting oxycodone preparations.

Despite the fact that hydrocodone has been available for clinical use in the US since 1943,[22] its metabolism and

kinetics are not entirely understood. Its primary metabolites are norhydrocodone (via cytochrome P450 [CYP]3A4) and hydromorphone (via CYP2D6). Hydromorphone is more potent and also much more tightly bound to the μ-opioid receptor than hydrocodone, and probably represents the active metabolite of hydrocodone. Therefore, patients who are ultrarapid CYP2D6 metabolizers may convert significantly more hydrocodone into hydromorphone, and there is a case report of an ultrarapid metabolizer developing unpleasant side effects after a single dose of a hydrocodone-containing analgesic following minor surgery.[23] With greater numbers of patients taking larger doses of hydrocodone, the rate of such adverse events will likely go up. Conversely, a poor CYP2D6 metabolizer would not expect to obtain analgesia except with higher hydrocodone doses.

Another rare side effect of hydrocodone administration is sensorineural hearing loss, which has been reported in patients taking hydrocodone, especially at high doses.[24,25] In these cases, the hearing loss did not respond to discontinuation of hydrocodone or to corticosteroid therapy. With higher doses of hydrocodone, this could become a significant risk.

Conclusion

The pending availability of long-acting oral hydrocodone medications will add another type of long-acting opioid medication to the chronic pain armamentarium. Despite education requirements including risk evaluation and mitigation strategy and safety features such as tamper-resistance, the benefits and liabilities of long-acting hydrocodone will ultimately need to be determined by the individual physician and the individual pain patient. Prudence and adherence to best practices in opioid prescribing will be essential to allow patients to benefit from pain-relieving properties of these medications without being harmed by their potential for abuse. Given the medical community's recent experience with chronic opioid therapy and potent opioids, it is incumbent on every prescriber to recognize the risks of abuse and diversion associated with these types of medications and to prescribe only for suitable patients with appropriate indications, while taking appropriate steps to monitor compliance and patient safety. Important stakeholders in society have already made it clear that they will be observing the impact of these new medications. For example, Senator Charles Schumer of New York wrote a letter to the FDA chairman in January, 2012, expressing his concern about the abuse potential of long-acting hydrocodone medications and asking whether the agency was doing enough to combat the prescription drug epidemic.[26]

On a broader level, it is clear that adding one more opioid medication, long-acting or not, tamper-resistant or not, will not solve chronic pain issues. The pharmacogenetics of pain go far beyond metabolism, and include the role of catecholamine O-methyl transferase polymorphisms in opioid response and abuse and opioid receptor subtypes and polymorphism.[27] In addition, the epigenetics of pain is a new and largely undefined field of research which may help explain why some pain becomes chronic and how pain medications can help or worsen pain conditions.[28] Until research is able to help doctors distinguish patients who are likely to respond well to chronic opioid therapy from those who are prone to develop worsening pain or addictive behaviors, it is important to offer pain patients a multidisciplinary treatment approach which maximizes outcomes while minimizing the risks and harms associated with pain treatment. Some patients are predisposed to bad outcomes due to genetic and other factors. Some pain conditions tend to worsen with opioid treatment. These patients should not be started on chronic opioid therapy. There is no evidence that chronic opioid therapy is helpful for these patients. For patients in whom we decide that chronic opioid therapy, as part of their multidisciplinary therapy, is a good choice because the benefits outweigh the risk, long-acting opioids are a good choice. The main goal for these patients is to increase their function. There is currently no safe chronic opioid option.

When considering patients for long-acting hydrocodone, the authors would advise to follow clear negative prognostic factors that have been established for chronic opioid treatment and include patients in an unstable or abusive living situation or with inadequate support, patients with poorly defined pain complaints with limited response to moderate opioid dosages, or those with somatoform disorders. Multidisciplinary pain medicine treatment appears to enhance adherence and decrease adverse events.[29]

Disclosure

The authors report no conflicts of interest in this work.

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