Introduction

Opioid Therapy in 2012: A Call for a High Degree of Attention to Detail

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Determining the number of patients with pain in the U.S. has been a difficult task because calculations of the prevalence of pain vary depending on the definitions of the levels of pain and on the methods used to quantify it. Recently, however, the Institute of Medicine estimated that in 2011 there were 100 million individuals with pain in the U.S.1 This calculation was made based on a study that used the World Health Organization’s World Mental Health Surveys instrument in 10 developed countries and concluded that approximately 37% of adults have common chronic pain conditions.2 It is noteworthy that this number includes neither patients with acute pain nor children with pain. The high prevalence of pain has led to an increase in the use of prescription analgesics, including opioids. The National Health and Nutrition Examination Survey showed an increase in the percentage of Americans using opioids from the period 1988–1994 (3.2%) to the period 2005–2008 (5.7%).1 Of these individuals, 7% were patients aged 65 years or older. Moreover, according to the White House Action Plan, the number of opioid prescriptions dispensed by retail pharmacies increased by an astounding 48%, to 257 million prescriptions between 2000 and 2009.3 Of the 3.61 billion prescriptions filled in the U.S. in 2009,4 7% were for opioids. Clearly, opioid analgesic use among Americans, and particularly in individuals aged 65 years and older, has increased in the past 12 years. This increase in opioid use can be explained in part by the progressively increasing number of patients experiencing pain as a result of osteoarthritis as the “baby boomer” generation has reached the age at which they begin to feel the effects of such a condition.5

Moreover, recent pain therapy recommendations for geriatric patients suggest that the use of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors may be associated with an increase in cardiac and gastric morbidity and mortality, resulting in a switch to more opioid analgesics being prescribed for pain treatment in these patients.6 It is predicted that the segment of the population aged 65 years and older will grow 35%, from 40 million in 2010 to 54 million in 2020. A parallel increase in opioid prescribing for patients in this age group can be expected. Therefore, the articles by Dr. Gudin and Dr. Brennan in this supplement of the Journal of Pain and Symptom Management are very timely and relevant. Their presentations not only describe the epidemic of adverse drug reactions and interactions, along with the estimated cost of these consequences, but also draw our attention to the increase in the number of emergency department visits and increase in the length of hospitalization for patients treated with opioids metabolized by the same oxidative enzymatic system as concomitantly administered medications prescribed for hypertension, high cholesterol, depression,
dysrhythmias, and the like. In light of these findings, it has become critically important for the clinician prescribing opioids to consider three factors beyond the benefit of pain relief: the metabolic pathways of the available opioids, the enzymatic systems used in the hepatic and intestinal metabolism by medications synchronously prescribed to treat other conditions, and the patient’s genetic characteristics that may yield rapid, slow, or poor metabolism of various drugs, including opioids.

The aforementioned considerations are particularly important to address in older adults; a recent meta-analysis of 43 studies of short-term opioid use among patients aged older than 60 years with chronic noncancer pain found that these individuals had reductions in pain intensity and improvements in physical functioning but at a cost of a decrease in mental health functioning. Based on the results of the reviews by Gudin and Brennan, it is tempting to suggest that the decrease in mental health function may be, at least in part, the result of drug-drug interactions. The reasoning is that the use of inhibitors of the CYP3A4 isoenzyme, detailed in Table 3 of the Gudin review, concomitantly administered with opioids metabolized by these pathways, could result in higher than expected plasma concentrations of the opioid, leading to central nervous system side effects. Consequently, it is important for clinicians to understand the alternative biotransformation processes that opioids must undergo before they are eliminated from the body. As discussed by Gudin, opioid metabolism may occur via oxidation (Phase I metabolism), glucuronidation (Phase II metabolism), or via a combination of the two. For the most part, the hepatic enzymatic pathways involved in Phase I opioid metabolism include the CYP2D6 and CYP3A4 isoforms. The latter is responsible for the metabolism of more than 50% of all drugs, and there is a high risk of drug-drug interactions within this system. Moreover, recent data suggest that the major metabolic pathway for methadone is the CYP2B6 isofrom, adding one more layer of complexity to an already complex issue. The investigations of Totah et al. suggest that total plasma levels and the ratio of methadone plasma isomers are controlled by the CYP2B6 isoform with an additional contribution by the CYP3A4 isoform. The genes expressing these two isoenzymes are each polymorphic, leading to the potential for significant variations in the rates of clearance, production of metabolites, analgesic effects, drug-drug interactions, and incidence of side effects in humans. Consequently, these genetic characteristics may explain, in part, the challenges that clinicians have faced when using methadone for chronic pain control.

The medical community continues to move toward individualization of medical therapy, not only to improve the quality of analgesia, in the case of pharmacologic pain therapy, but also to decrease the costly human and economic effects of drug-drug interactions. Pain therapy should be individualized, wherein the most appropriate opioid and adjuvant medications are selected based on their metabolic pathways. When using opioids metabolized via oxidation, clinicians should conduct an analysis of the medications that a patient is already receiving that could potentially inhibit these enzymatic pathways. Future studies will help us understand which haplotypes of the various nucleotide polymorphisms directly affect Phase I metabolism of not only opioids but also of adjuvant analgesics to minimize the impact of drug-drug interactions and/or to decrease clearance. In the interim, it would seem prudent to favor opioids cleared via Phase II metabolism, to avoid these intricate issues in patients treated with medications already highlighted as inhibitors of these enzymatic pathways.

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