Analgesics

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Outline

Introduction

Chronic pain affects about 100 million adults in the United States—more than those affected by heart disease, cancer, and diabetes combined.[1] The consequences of uncontrolled pain are broad including negatively impacting health, functional status, well-being, and quality of life. Obesity correlates highly with certain chronic pain conditions including osteoarthritis and fibromyalgia. The mechanisms behind this are not well described but may be related to increased mechanical stress as well as induction of chronic inflammatory states.[2] As the prevalence of obesity increases, the need to dose analgesics in obese patients will become more prevalent. In this chapter, we will review the data and discuss dosing of several different classes of analgesics in obesity including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), adjuvants, and opioids.

Acetaminophen

Acetaminophen is an analgesic and antipyretic discovered in the late 1800s. Despite over a century of use in medicine, its mechanism of action as an analgesic is still not completely understood. Acetaminophen is widely distributed through most body tissues except fat with an estimated volume of distribution (V_d) of 0.7 to 1.1 L/kg. It is approximately 10% to 25% protein bound.[3,4] Acetaminophen's metabolism is of particular

clinical interest. It is approximately 90% metabolized via saturable glucuronidation and sulfation pathways. Less than 5% is excreted unchanged in the urine.[4] The remaining 5% to 10% is metabolized via cytochrome P450 (CYP) 2E1 to an active metabolite, N-acetyl-p-benzoquinone imine (NAPQI). In normal metabolism, NAPQI then conjugates with glutathione (GSH) to form an inert metabolite before excretion. In overdose, glucuronidation and sulfation pathways become saturated, forcing acetaminophen to metabolism via CYP2E1.[3] The increased formation of NAPQI eventually depletes the body's GSH stores, and the remaining NAPQI accumulates in hepatocytes and leads to acute liver failure (ALF).

With acetaminophen in many over-the-counter (OTC) analgesic products as well as in several prescription combination products, the risk for exceeding the daily maximum dose of acetaminophen is high. As a result, unintentional or intentional misuse of acetaminophen is the leading cause of ALF in the United States.[5] Interestingly, data evaluating the effect of obesity on acetaminophen focus both on general pharmacokinetics (PK) and obesity's potential effect on induced hepatotoxicity.

Pharmacokinetic Models

Two animal studies have evaluated the PK of acetaminophen in overfed rat models. In the first study, obese and control animals were dosed with 136.5 mg of acetaminophen intravenously (IV) as a flat dose.[6] Data showed reduced concentrations of sulfate metabolites in obese rats as well as lower overall acetaminophen concentrations. Interestingly, clearance of acetaminophen was 27% higher in obese animals compared to controls, suggesting an alteration of elimination via increased drug metabolism. When adjusted for total body weight (TBW), the difference in clearance normalized, indicating increases in metabolic rate were roughly proportional to increases in body size.

The second study also used an overfed rat model.[7] In this study, animals were administered one dose of acetaminophen 287 mg/kg based on TBW. Some results were similar to the first study. Sulfate metabolism was significantly reduced to approximately 41% of lean controls, and this seemed to be compensated by a resultant increase in glucuronide metabolism. However, this balanced overall to no change in total body clearance, which differs from the increased metabolism found in the prior study. Plasma acetaminophen concentrations also differed between studies, with this study finding initial concentrations to be similar before developing significantly elevated concentrations in obese animals over the subsequent 8 hours of observation. The reason for differences between the studies is unclear, but it may be related to differences in dosing (flat dose versus weight-based).

In humans, three studies have evaluated acetaminophen PK in obesity.[8-10] No study identified differences in half-life between obese and control patients. Although most studies (both animal and human) identified no change in V_d, one human study suggested there was a partial, but not complete, distribution of acetaminophen into excess weight above ideal body weight (IBW) and suggested a correction factor of 0.44 times IBW for men and 0.31 times IBW for women.[9] One study evaluated plasma concentrations and found obese patients had a lower area under the curve as maximum plasma concentrations were reached at a later time and were significantly lower.[8]

Two of the three studies reported increases in acetaminophen clearance in obese patients, which normalized when corrected for TBW, again indicating a proportional increase in clearance with increasing body weight.[9,10] One study compared this acetaminophen clearance to clearance of lorazepam and oxazepam, both of which are exclusively metabolized via glucuronide conjugation.[10] Clearance of lorazepam, oxazepam, and acetaminophen were highly correlated, suggesting an increase in glucuronide conjugation capacity in obese subjects,