Impact of Morphine Metabolite Differences on Analgesia in Women and Men

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This study aims to explore the pharmacokinetic factors that may contribute to gender-specific differences in response to painful stimuli and alteration of response with opioid analgesics. Specifically, this study method will be used to assess the interaction of a parent drug with its active metabolites and used to quantitate the interaction of morphine with its glucuronide metabolites in female and male volunteers. The primary hypotheses are that alterations in the relative amount of active metabolite morphine-6-glucuronide (M6G) produced by an individual will alter the analgesia response of morphine and, that alterations in morphine-3-glucuronide (M3G) also affect analgesia because it impacts the amount of active metabolite, M6G, that can be created. Since women undergo regular fluctuations in gonadal hormones that can alter metabolites formation, the consequences of this are greater for them. This study will (1) assess the impact of morphine metabolites on analgesia in women and men during stable gonadal hormone levels, and (2) assess the impact of morphine metabolites on analgesia in women during fluctuating gonadal hormone levels. After IRB approval, 10 male and 10 female subjects, ages 18-40, were recruited for this two-period crossover study. During one session, subjects receive 50 mg of ranitidine IV 30 minutes before the session, followed by a target controlled infusion of morphine maintained for 1 hour then an increased target concentration of morphine held for 1 hour. In the crossover session, each subject receives a saline infusion rather than the ranitidine dose. The target concentration levels are replicated in both sessions. The results of this study will identify the role that morphine metabolites play in contributing to acute analgesia from morphine and determine the impact that gonadal steroid hormones have in modulation of these effects. This knowledge can then be used to determine the clinical implications of these factors for providing adequate analgesia in females compared to males.