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Articles You Might Have Missed

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Isbister G, Calver L, Page C, et al. Randomized Controlled Trial of Intramuscular Droperidol Versus Midazolam for Violence and Acute Behavioral Disturbance: The DORM Study. Ann Emerg Med 2010; 56:392–401

Background: Droperidol was used frequently for chemical sedation in agitated and/or violent patients until it received a blackbox warning for QT prolongation and torsades des pointes from the FDA in 2001. Debate remains regarding the most ideal medication for sedation in the ED.

Research Question: Is intramuscular administration of droperidol, midazolam, or a combination of these drugs safer and more effective at achieving sedation in agitated patients?

Methods: This is a blinded randomized controlled trial conducted in an urban ED of adult patients who presented with undifferentiated agitated behavior and required both physical restraints and chemical sedation. The duration of the acute behavioral disturbance was a primary outcome. Secondary observations, including vital signs, ECGs, adverse events, staff injuries, and Altered Mental Status Scale scores, were performed for 6 h following study drug administration. Additional sedation was administered at the discretion of the attending physician.

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Results: Of 223 eligible patients during the 1-year study, 91 were included. Thirty-three patients received droperidol, 29 received midazolam, and 29 received both medications. The median duration of behavioral disturbances was 20 min for droperidol alone, 24 min for midazolam alone, and 25 min for the combination. A hazard ratio of 2.31 (95% CI, 1.01 to 4.71) was determined for additional medication requirements for midazolam versus droperidol. Adverse medication effects were more common in the midazolam group (primarily oxygen desaturation). QT prolongation occurred infrequently and equally in each treatment group and there was no mention of dysrhythmia.

Conclusion: Intramuscular droperidol is a safe option for the treatment of agitated patients in the ED compared to intramuscular midazolam which is associated with unpredictable effects and a higher incidence of oxygen desaturation.

Critique: Strengths of the study include the randomized, blinded design. Weaknesses include the lack of weight-based dosing of study medications and the choice of duration of behavioral disturbance rather than a sedation scale score as primary outcome. Most subjects were alcohol intoxicated. So, the safety and effectiveness of droperidol may not be generalizable to a population where other substances may be more prevalent. In such a population, droperidol might be less effective and result in more adverse events. Also, midazolam dosing in this study may be excessive, introducing bias with respect to its safety profile.

Implication for Toxicologists: This study provides support that droperidol is a safe and effective option for the sedation of acutely agitated patients in the ED.

Belze O, Legras A, Ehrmann S, et al. Cannabis-Induced Acute Pancreatitis. Am J Emerg Med 2011; 29:131.e3–131.e4

Background: The most common causes of pancreatitis are alcoholism and cholelithiasis.

Abstract: A 17-year-old male presented with abdominal pain and status epilepticus. His serum lipase was elevated at 1,211 IU/L. An abdominal US demonstrated a normal appearing gallbladder without stones. His Ranson's score was 1. CT imaging of the abdomen performed 48 h after presentation showed acute pancreatitis, hepatopancreatic necrosis, and ascites. Serum testing for HIV, hepatitis serologies, EBV, CMV, parvovirus B19, and mumps were negative. His cholesterol, serum triglycerides, calcium, PTH, and 25-hydroxy vitamin D levels were normal. Testing for cystic fibrosis was negative. No intracranial pathology was identified on head CT.

Conclusion: After excluding other medical etiologies and noting improvement with tobacco and cannabis cessation, the etiology of the patient's pancreatitis was attributed to chronic cannabis use. Five other cases of cannabis-induced pancreatitis have been reported in the medical literature. The pathophysiology remains unknown.

Critique: As reported, the case lacks scientific rigor. Readers might appreciate more clinical and laboratory details (such as the reference range for lipase). The Ranson score is unimpressive. The authors never address the etiology of status epilepticus nor consider toxins that might cause both seizures and pancreatitis.

Implication for Toxicologists: Although rare, cannabis use should be considered as a potential etiology of pancreatitis when more common etiologies have been excluded.

Devarbhavi H, Dierkhising R, et al. Single-Center Experience with Drug-Induced Liver Injury from India: Causes, Outcome, Prognosis, and Predictors of Mortality. Am J Gastroenterol 2010; 105:2396–2404

Background: Due to its critical role in drug metabolism, the liver may be susceptible to toxic injury, resulting in morbidity and mortality. In many instances, liver injury is subclinical, making the actual incidence difficult to determine.

Research Question: What are the causes, outcome, and predictors of mortality in patients with drug-induced liver injury?

Methods: This was a retrospective analysis of a dedicated database of patients with drug-induced liver injury (DILI) at St. John's Medical College Hospital, Bangalore, India. Criteria for inclusion were a documented exposure to a drug that produced hepatotoxicity (bilirubin of at least 2 mg/dL, AST more than three times the upper limit of normal, or alkaline phosphatase greater than two times the upper limit of normal at time of admission), and exclusion of other causes. Patients were followed for 6 months or until normalization of LFTs.

Results: Three hundred thirteen cases of DILI were identified from the database that spanned 12 years; 58% were males and 42% were females. The responsible drugs were used for a mean of 54.4 days, and those most frequently cited were anti-tuberculous drugs (ATD), phenytoin, olanzapine, and dapsone. Using the Roussel Uclaf Causality Assessment Method diagnostic scale, 25% of cases were determined as highly probable and 49% as probable etiologies. A total of 54 patients (17.3%) died due to DILI. There was a higher incidence of jaundice, icterus, ascites, and ingestion of ATD among patients who died. Significant elevations in INR, creatinine, and MELD scores were also noted in deceased patients. The presence of encephalopathy with a prolonged prothrombin time (>31.5 s), encephalopathy with a prothrombin time (<31.5 s) and ascites, and a low albumin (<1.65 g/dL) in non-encephalopathic patients predicted death.

Conclusion: High MELD scores, ascites, encephalopathy, low albumin, and elevated prothrombin time are associated with significant mortality in drug-induced liver injury.

Critique: This is a retrospective study conducted at a single center, and prospective validation is warranted. Geographic differences in the standard of care, use of traditional remedies, medications responsible for DILI, and treatment options, including liver transplantation, may affect the generalizability of the results of this study. Outcome variables such as fulminant hepatic failure and ascites are poorly defined. Regarding laboratory parameters, it is not clear if the cited values are those from initial presentation or peak abnormalities.

Implication for Toxicologists: This study demonstrates that the etiology and demographics of DILI vary geographically. It confirms previous knowledge regarding risk factors for mortality in patients with DILI.

Hatch E, Troisi R, Wise L, et al. Preterm Birth, Fetal Growth, and Age at Menarche Among Women Exposed Prenatally to Diethylstilbestrol (DES). Reprod Toxicol 2011, doi:10.1016/j.reprotox.2010.11.006

Background: The use of DES, a purported treatment for preterm birth, ceased in 1971 when it was associated with the development of vaginal adenocarcinoma in women exposed in utero. Other effects from prenatal exposure have not been fully investigated.

Research Question: Is there a difference in the gestational length, fetal growth, and age at menarche in women exposed in utero to DES?

Methods: An analysis of data from two previous cohort studies (National Cooperative DES Adenosis and a University of Chicago clinical trial) was used to assess the effects of prenatal DES exposure. Data regarding the dose of DES and time of exposure was known in 39% and 81% of women, respectively. The total dose was stratified into high- and low-dose groups. Multivariable linear regression analysis was used to assess the effect on gestational length and birth weight while controlling for

confounders. Moreover, logistic regression was utilized to assess the risk of small for gestational age (SGA), preterm birth, and the association with the premature onset of menarche.

Results: DES exposure was associated with a slightly shorter gestation (−0.63 weeks; 95% CI, −0.78, −0.49), preterm delivery defined as <37 weeks (OR, 2.97; 95% CI, 2.27, 3.87), reduction in birth weight (−105 g; 95% CI, −134, −76), increased risk of an SGA birth (OR, 1.61; 95% CI, 1.31, 1.98) and earlier menarche defined as ≤10 years (OR, 1.41; 95% CI, 0.97, 2.03).

Conclusion: Prenatal DES exposure in this analysis was associated with a slight reduction in mean birth weight and gestation length, an increase in preterm delivery and small for gestational age births, and a slightly increased risk of early menarche. It is speculated that a disruption of hormones during pregnancy and stress due to the exogenous administration of estrogen may be responsible.

Critique: Due to the retrospective nature of this study, recall bias may influence the results. Unidentified environmental exposures in the study participants and their mothers may be confounders. While the study found statistically significant differences, there may not be biologically relevant differences (i.e., gestational age).

Implication for Toxicologists: Exogenous estrogen exposure in utero from agents such as DES may have untoward immediate and delayed effects.

Conflict of Interest No funding or conflicts of interest to disclose.