Articles You Might Have Missed

Nathan Menke · Andrew King · Anthony Pizon

Published online: 26 March 2013
© American College of Medical Toxicology 2013

Keywords Verapamil · Cyclodextrin · N-acetylcysteine · Pediatric acute liver failure · Azithromycin · Sudden cardiac death · Dexmedetomidine · Withdrawal syndrome · Clonidine

Mottram A, Bryant S, Aks S. Dose-dependent response to cyclodextrin infusion in a rat model of verapamil toxicity. West J Emerg Med. 2012; 13(1):63–7.

Background: Cyclodextrins (CD) are hydrophilic oligosaccharides that are widely used as excipients to increase drug solubility and stability but may also have utility in enhancing elimination and decreasing xenobiotic toxicity. Much like one of the proposed mechanisms of intralipid use, CD has the potential to create an intravascular sink. Sugammadex, a CD that effectively reverses the effects of rocuronium, exemplifies this mechanism of “detoxification.” A previous study undertaken by the same authors demonstrated worse survival times with administration of a sulfobutylether-beta-cyclodextrin (SBE-CD) to verapamil-poisoned rats. The authors attributed this effect to the cyclodextrin’s hyperosmolar load.

Research Question: Does SBE-CD decrease time to death in a verapamil-poisoned rat model?

Methods: This was a prospective, unblinded randomized, controlled study. After induction, male Wistar rats were infused with verapamil (32 mg/kg/h) and varying concentrations of SBE-CD premixed in the same infusion bag. A control group and four treatment groups were administered verapamil and SBE-CD with molar ratios of 1:1, 1:2, 1:4, and 1:8. Osmolarity varied between 300 and 352 mOsm/L. The primary endpoint was time to asystole.

Results: Time to asystole was prolonged in the 1:4 ratio group when compared to control (21.2 vs. 17.6 minutes, $p=0.05$). No other intervention group demonstrated a statistically

significant difference in time to asystole. There were no differences in time to apnea, but apnea preceded arrest by several minutes in all groups.

Conclusion: At a molar ratio of 1:4, a verapamil–SBE-CD infusion demonstrated statistically significantly increased time to asystole.

Critique: Overall, this is an interesting but negative study. The lack of a dose response suggests that the SBE-CD was unlikely to be responsible for the increased time to asystole in the 1:4 group. As no power calculation was provided, the lack of efficacy may also be due to an inadequate number of subjects per group. Limitations include the premixing of verapamil and SBE-CD and co-infusion (an artificial model of human poisonings), lack of invasive hemodynamic monitoring, and apnea preceding cardiac arrest in all groups. Finally, as with all animal studies, the applicability to human physiology is unclear.

Implication for Toxicologists: Intravascular sequestration of toxic xenobiotics is an intriguing mechanism for the potential treatment of many xenobiotics. Although mechanistically plausible, little weight can be placed on this potential intervention until further investigation supports improved outcomes.

Squires R, Dhawan A, Alonso E, Narkewicz M, Shneider B, Rodriguez-Baez N, et al. Intravenous N-acetylcysteine in pediatric patients with non-acetaminophen acute liver failure: a placebo-controlled clinical trial. Hepatology. 2012 [doi 10.1002/hep.26001].

Background: The etiology of non-acetaminophen (APAP) acute liver failure (ALF) differs between children and adults; the utility of N-acetylcysteine (NAC) in the pediatric non-APAP liver failure patient has not been previously assessed. A previous randomized-controlled study in adults with non-APAP liver failure had demonstrated improved transplant-free survival in adults with low-grade

N. Menke (✉) · A. King · A. Pizon
UPMC, Pittsburgh, PA, USA
e-mail: menkenb@upmc.edu

encephalopathy in patients treated with NAC. In children, NAC has suggested benefit in at least one single-center retrospective review.

Research Question: Does NAC improve survival in non-APAP ALF in children?

Methods: This was a prospective adaptively allocated, doubly masked, placebo-controlled multicenter trial at established Pediatric Acute Liver Failure Study Group sites. Eligible children from birth to age 17 with non-APAP-induced ALF were enrolled. Of 607 patients, after assessment for eligibility, a total of 184 children were enrolled and administered 150 mg/kg/day or placebo (D5W alone) for up to 7 days. The primary outcome was survival at 1 year. Secondary outcomes were transplantation-free survival, transplantation, ICU and hospital stays, organ system failure, and maximum grade of hepatic encephalopathy (HE).

Results: Although the 1-year survival did not differ significantly between the NAC (73 %) and placebo (82 %) groups ($p=0.19$), the 1-year transplant-free survival was lower in the NAC group as compared to placebo (35 vs. 53 % $p=0.03$, respectively). Median time to NAC administration was 3 days. Nontransplanted children less than 2 years old, with HE grade 0–1, had lower rates of survival if they received NAC (25 vs. 60 %; $p=0.0493$). There was no difference in the secondary outcomes studied. Post-transplant deaths did not differ.

Study Conclusion: Continuous infusion of NAC at 150 mg/kg/day given to children with non-APAP ALF did not improve survival and may be harmful. It is hypothesized that NAC may blunt necessary and restorative pro-inflammatory responses at a critical time or that NAC may suppress hepatic regeneration. Broad use of NAC in non-APAP pediatric acute liver failure may be harmful, especially in children less than 2 years of age.

Critique: The most common etiologies of ALF vary by age. Therefore, without adequate subgroup analysis to account for the heterogeneity (both age and etiology of ALF) in the study population, broad application of the study results to all children less than 18 years of age is inappropriate. The etiologies of ALF and physiology in older children are likely to be more closely aligned to adults; NAC has been shown to be beneficial in this group. The study suggests unclear effects at intermediate ages and the potential for a threshold at which the risk/benefit ratio shifts. Thus, more data are needed.

Implication for Toxicologists: Use of NAC in adults with ALF continues to be the standard of care. However, in children less than 2 years of age with ALF from indeterminate diagnosis, NAC should be used with caution, if not discouraged. Some clinicians may use this study as evidence for withholding NAC in all children with ALF of indeterminate etiology. However, we feel that more evidence is required to support that argument.

Ray W, Murray K, Hall K, Arbogast P, Stein C. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012;366(20):1881–90.

Background: Erythromycin, in contrast to azithromycin (AZM), has been associated with QT prolongation, torsades de pointes, and sudden death via blockade of delayed rectifier potassium channels. A number of case reports have linked AZM to QT prolongation, ventricular dysrhythmias, and sudden cardiac death.

Research Question: Does AZM have an increased risk of sudden cardiac death?

Methods: This was a retrospective cohort observational study. The study cohort was composed of individuals registered with the Tennessee Medicaid program who had been prescribed AZM from 1992 to 2006. Medicaid pharmacy files were used to identify antibiotics and other medications filled. Exclusionary criteria included life-threatening noncardiovascular illness, diagnosis of drug abuse, nursing home occupation, or hospitalization within the previous 30 days. The authors included four frequency-matched “control periods” per AZM exposure during which there was no use of antibiotics. The authors also utilized cohorts of patients that received amoxicillin, ciprofloxacin, and levofloxacin as comparison groups. The primary endpoints were cardiovascular death and death from any other cause.

Results: 347,795 AZM prescriptions, 1,391,180 control periods, 1,348,672 amoxicillin prescriptions, 264,626 ciprofloxacin prescriptions, and 193,906 levofloxacin prescriptions were included in the analysis. Azithromycin was associated with an increased risk of death as compared to control during that 5-day interval of presumed ingestion. The hazard ratio was 2.88 for cardiovascular death (95 % CI 1.79 to 4.63; $p<0.001$). AZM had a greater risk of CV deaths as compared to both amoxicillin and ciprofloxacin (hazard ratio, 2.49, $p=0.002$, and 3.48, $p=0.01$, respectively). Amoxicillin, ciprofloxacin, and levofloxacin were not found to be associated with cardiovascular death when compared to antibiotic-free periods. When AZM was compared to levofloxacin, there was no significant difference in risk of cardiovascular death.

Conclusion: Azithromycin is associated with an increase in cardiovascular death compared to amoxicillin and ciprofloxacin, as well as periods of time when no antibiotics were prescribed. There was no difference in risk of death when AZM was compared to levofloxacin.

Critique: As with any cohort study, associations cannot establish causality. The authors took great pains to minimize confounders and had a large cohort; however, there is a selection bias implicit in the study. The results are in concordance with what is known about antibiotics in the same class (erythromycin and clarithromycin).

Implication for Toxicologists: This challenges the widely held belief that AZM carries no risk of cardiotoxicity. Similar medications (erythromycin and clarithromycin) carry cardiovascular risk similar to those observed in this study, implying that the cardiotoxicity associated with AZM is true. The study does not address the absolute benefit/risk of AZM. However, clinicians should be aware of the small, but likely increased, risk of sudden cardiac death associated with prescribing AZM.

Kukoyi A, Coker S, Lewis L, Nierenberg D. Two cases of acute dexmedetomidine withdrawal syndrome following prolonged infusion in the intensive care unit: Report of cases and review of the literature. Human and Experimental Toxicology. 2013;32(1):107–10.

Background: Dexmedetomidine (DEX) has received a fair amount of attention and increased use by anesthesiologists, intensivists, and emergency department physicians as a quick-acting sedative–anesthesia agent. As with clonidine, DEX's short duration of action introduces the risk of a withdrawal syndrome. This withdrawal has been reported previously in pediatric patients. Use of a less-sedating imidazoline, clonidine, mechanistically makes sense when treating withdrawal from DEX.

Research Question: Is there a withdrawal syndrome associated with DEX? Does clonidine effectively treat DEX withdrawal?

Methods and Reports: Case series.

Case 1. A 61-year-old woman was admitted with sepsis due to ascending cholangitis. She had no history of alcohol, opiate, or benzodiazepine use or abuse. She was initially sedated with fentanyl, 100 µg/h; midazolam, 2 mg/h; and propofol, 75 µg/kg/min. Beginning on ICU day 3, the patient was placed on a DEX infusion that lasted for 168 h. Six hours after discontinuation of the DEX, she developed agitation, hypertension, and tachycardia. The patient received haloperidol and metoprolol without effect. Upon administration of clonidine, 0.2 mg tid, improvements

in vital signs and mental status were observed within 12 h. The clonidine was tapered off over several days (0.1 mg/day reduction).

Case 2. A 46-year-old woman was admitted for induction chemotherapy for cervical granulocytic sarcoma. She had no history of alcohol, opiate, or benzodiazepine use or abuse. Five days following her first cycle of chemotherapy, she developed neutropenic fever treated with antibiotics and intubation. Initially, she was sedated with 100 µg/h fentanyl and midazolam 2 mg/h. On ICU day 2, she underwent surgical resection of an infected cecum. On ICU day 3, midazolam was weaned off. On ICU day 11, the fentanyl infusion was discontinued, and a DEX infusion was started in anticipation of extubation. On ICU day 16, she was weaned off of the DEX over 6 h, after a total of 144 h of DEX. She developed tachycardia (120–150 bpm), hypertension (120/80–150/100), intermittent fevers, diaphoresis, mydriasis, and agitation for 5 days. She was diagnosed with hyper-sympathetic syndrome and was placed on an oral clonidine taper over 4 days (0.1 mg clonidine tid, then bid, then qd). She had mild improvement in her HR and BP after institution of the clonidine. She was discharged 24 h after conclusion of the taper.

Study Conclusion: Oral clonidine is an efficacious treatment for sympathomimetic signs and symptoms due to DEX withdrawal.

Critique: Implicit in the nature of case reports/series is the limited ability to draw significant conclusions. Given the mechanistic similarity to clonidine, it is not surprising that DEX may have a similar withdrawal syndrome. Oral clonidine seemed to be effective in treating DEX withdrawal. The total dose and/or duration of DEX infusion that places a patient at risk for withdrawal requires further study. Optimal use of clonidine to treat DEX withdrawal also requires further study.

Implication for Toxicologists: Toxicologists may be consulted to aid in managing DEX withdrawal. Clonidine should be considered as a primary means to control suspected withdrawal from DEX.