Articles You May Have Missed

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Introduction

In this issue of the *Journal of Medical Toxicology*, a new feature section entitled “Articles You May Have Missed” is introduced. The goal of this new section is to highlight articles from non-mainstream toxicology journals that may impact the practice of toxicology. The selected articles will cover a broad range of topics within the scope of toxicology including basic science, environmental/occupational exposures, and acute care toxicology. The format consists of a structured synopsis, brief critique, and comments on the potential implication of the information for medical toxicologists. Four articles will be presented in each issue.

Mitchell AM, Jones AE, Tumlin JA, Kline JA (2010)
**Incidence of contrast-induced nephropathy
after contrast-enhanced computer tomography
in the outpatient setting. Clin J Am Soc Nephrol 5:4–9**

Background: Prior investigations of contrast-induced nephropathy (CIN) involve hospitalized patients and focus on angiography. No prior studies have targeted the outpatient setting where contrast-enhanced CT scan use has dramatically increased in recent years.

Research Question: What is the incidence of CIN in outpatients undergoing contrast-enhanced computer tomography?

Methods: Investigators prospectively followed a consecutive cohort of emergency department patients that underwent intravenous contrast-enhanced CT. The primary outcome was an increase in serum creatinine (≥ 0.5 mg/dL or $\geq 25\%$ increase from baseline) within 2–7 days following contrast administration. Secondary outcomes included severe renal failure (creatinine ≥ 3.0 mg/dL or need for dialysis) or renal failure contributing to death within 45 days.

Results: During the 2-year study, 11% (70/633) of subjects developed CIN. One percent (6/633) of subjects developed renal failure, with five requiring hemodialysis. CIN was felt to cause four deaths. The relative risks of renal failure and death after contrast-enhanced CT were 48 and 64, respectively, compared to non-contrast scans. Analysis failed to show increased CIN with traditional risk factors such as pre-existing renal insufficiency. Subgroup analysis did not show a treatment benefit for sodium bicarbonate pretreatment.

Conclusion: The incidence of CIN is higher in outpatients than previous reports and carries significant risk of morbidity and mortality.

Critique: This well-designed and executed study demonstrates a significant risk associated with the administration of intravenous contrast material for CT scanning. The authors present a cogent discussion on the plausible mechanistic differences of CIN in the outpatient versus inpatient setting.

Implication for Toxicologists: CIN in the acute setting is an ideal milieu for a well-designed study of *N*-acetylcysteine prophylaxis.

**Marchetti A, Rossiter R (2009) Managing acute
acetaminophen poisoning with oral versus intravenous
N-acetylcysteine: a provider-perspective cost analysis.
J Med Economics 12:384–391**

Background: Both oral (po) and intravenous (iv) *N*-acetylcysteine (NAC) are efficacious for treating acetamin-

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open toxicity. Since both are effective, the selection of which route to use may then be based on other factors such as adverse effect profile or cost.

Research Question: The investigators sought to determine the cost difference between FDA-approved po and iv NAC treatment for acute acetaminophen toxicity treatment.

Methods: The authors developed a comprehensive cost model that included clinical course, clinical outcome, and adverse events of NAC therapy. Clinical factors were assigned a probability of occurrence based on referenced literature reports and a cost value using institutional and published cost data.

Results: The investigators found an overall cost savings of approximately 33% with iv compared to po NAC therapy in all scenarios.

Conclusion: Intravenous NAC is more cost-effective than oral administration.

Critique: The study design is biased in favor of the iv protocol for several reasons. First and foremost, it utilized the FDA-approved treatment protocols that entail 3 days of po versus 1 day of iv NAC therapy. Pretty much any treatment whose duration is one third of the alternative in a hospitalized patient will be less expensive. Second, the inputted rate of anaphylactoid reaction (3%) associated with iv NAC may be low. This percent reflects experience with iv administration of the oral formulation (Mucomyst®), not the FDA-approved iv formulation (Acetadote®). Available data for Acetadote® regarding anaphylactoid reaction range between 2% and 17% (initial package insert, Whyte et al. (2007) *Curr Med Research Opin* 23:2359–2368 and Yarema et al. (2009) *Ann Emerg Med* 54:606–614). Lastly, the model failed to factor in emesis following iv NAC that occurs in 9% of cases (Whyte et al. (2007) *Curr Med Research Opin* 23:2359–2368).

Implication for Toxicologists: The toxicology community needs a more realistic cost analysis comparing the 24-h po versus 21-h iv NAC treatment protocols.

Frolich E, Samberger C, Kueznik T et al. (2009)

Cytotoxicity of nanoparticles independent of oxidative stress. *J Toxicol Sci* 34:363–375

Background: Nanotechnology has promising applications in medicine, but preliminary research also raises concern of potential health risks. Several studies demonstrate that nanoparticles can induce oxidant stress injury, but other cytotoxic mechanisms have not been evaluated.

Research Question: The authors tested the ability of nanoparticles to induce cell injury via non-oxidant stress pathways.

Methods: Human endothelial cells were exposed to polystyrene beads varying in size from 20 to 500 nm. Primary outcomes included chemical and histological markers of cell proliferation, apoptosis, cell membrane integrity, and

oxidative stress. Secondary outcomes included identification of vulnerable cell organelles.

Results: Cytotoxicity was directly related to cellular uptake of particles and inversely related to particle size. Cell proliferation, cellular energy content, and cell membrane integrity were decreased. Apoptotic markers increased. Nanoparticles induced minimal oxidant injury. Particles localized in endosomes, but not mitochondria.

Conclusion: Nanoparticles may injure cells independently of oxidant stress via mechanisms such as cell membrane disruption or apoptosis.

Critique: Once you get past some translation difficulties, this elegant and detailed study provides insight into the potential downside of nanotechnology and serves as an impetus for continued research and safety vigilance.

Implication for Toxicologists: Toxicologists must keep abreast of emerging or potential toxins that may be encountered in the public health and occupational domains of our specialty.

QuickStats (2009) Motor-vehicle traffic and poisoning death rates by age—United States, 2005–2006.

MMWR 58:753

Background: In studies of death due to injury, motor vehicle-related fatality has typically been the leading cause. Epidemiological studies in the current decade have shown an increase in poison-related fatalities.

Research Question: How does the incidence of death by motor vehicle compare to that of poisoning by age?

Methods: This CDC analysis used 2005–2006 mortality data from the National Vital Statistics System to compare the incidence of motor vehicle crash deaths to poisoning deaths by age.

Results: Poisoning deaths were more common than motor vehicle deaths for individuals 34–56 years of age. Poisoning deaths included drug overdose, misuse of drugs, and deaths associated with solid or liquid biological substances, gases or vapors, and “other” substances. However, of the deaths in the analysis, 92% involved drugs.

Critique: While the reader cannot fully scrutinize methodological details in this brief, the graphic data are remarkable: Poisoning has overtaken trauma as a leading cause of injury-related death in middle-aged adults.

Implication for Toxicologists: While abstracting poison center fatalities for the 2009 National Poison Data System, this author was struck by the preponderance of opioid misadventures. Although the CDC QuickStats data mention “drugs” only in broad terms, there is mounting epidemiological evidence (such as MMWR 2009;58:1171–1174) that allows toxicologists to confidently link a rise in opioid misadventures to the observed rise in poisoning death. These data highlights an opportunity for the toxicology community to intervene in an evolving epidemic.