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INDICATORS FOR SERIOUS KIDNEY COMPLICATIONS ASSOCIATED WITH TOXIC EXPOSURES: AN ANALYSIS OF THE NATIONAL POISON DATA SYSTEM

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Abstract

Context—Over two million poisoning exposures are reported to U.S. poison control centers annually. A broad population-based survey of toxic exposures and the correlated patterns of reported kidney injury (acute or chronic) have not been systematically characterized.

Objective—Our objective was to study the demographic and exposure patterns associated with indicators for serious kidney complications (ISKC), as defined by the variables in the NPDS.

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Declaration of Interest Statement:

The authors report no declarations of interest.

Disclaimer:

The American Association of Poison Control Centers (AAPCC) maintains the national database of information logged by the country's 57 poison control centers. Case records in this database are from **self-reported** calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, an inhalation, or a topical exposure, etc.), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

NOTE: All data produced from the American Association of Poison Control Centers databases during the year in which the exposures occur is considered preliminary. Changes occur in only a small number of cases each year. This is because it is possible that a poison center may update a case anytime during that year if new data is obtained. In the fall of each year the data for the previous year is locked and no changes are permitted. At that time the data for a year is considered closed.

Previous Publications:

This work has been presented as a platform presentation (Vilay AM, Wong CS, Schrader RM, Mercier RC, Seifert SA. Acute kidney injury related to toxic exposures. *Pediatr Nephrol* 25(9): 52, 2010) at the 15th Congress of the International Pediatric Nephrology Association, New York, NY, USA and as a poster presentation (Seifert SA, Vilay AM, Wong CS, Schrader RM, Mercier RC. Characterization of acute kidney injury in toxic exposures. *Clin Toxicol (Phila)* 48 (6): 615, 2010) at the 2010 North American Congress of Clinical Toxicology Annual Meeting Denver, CO, USA.

Materials and Methods—This was a retrospective, case-control study using the data elements available in the NPDS. We assessed data related to patient characteristics, substance exposure, and management. Cases and controls were derived from adult and pediatric exposures documented in NPDS (2001–2007) as having “renal effects.” For substance-specific analyses, cases were restricted to those involving single substances or single entity pharmaceutical preparations. ISKC cases presented with one or more of the following NPDS codes: increased creatinine, and/or oliguria/anuria, and/or renal failure. Controls were subjects with “renal effects” but did not have increased creatinine, nor anuria/oliguria, nor renal failure. Univariate and multivariate logistic regression analyses identified factors associated with ISKC and determined the relationship between these factors.

Results—From the approximate 16.8 million exposures reported to the NPDS within the study timeframe, there were 16,444 single substances exposures with renal effects of which 9,074 cases experienced ISKC (55.2%) compared to 7,370 controls without ISKC. Cases with ISKC tended to be males, adults, and reported to involve intentional exposures. Cases with ISKC had higher rates of reported hemodialysis/hemofiltration (27.7%; N=2,517) and death 10.9% (N=990) compared to controls respectively (2.1%; N=155) and (0.8%; N=60), $p<0.001$. Substances considered *a priori* to be nephrotoxic were associated with a higher risk of ISKC.

Discussion and Conclusion—The NPDS provided insight into the subjects and types of exposures that associate with ISKC. Subjects with ISKC experienced higher rates of morbidity and mortality compared to subjects without ISKC. We identified subject characteristics and classes of compounds associated with ISKC. We hope that the hypotheses generated from this study of the NPDS will raise awareness of the possible risk factors and complications associated with ISKC.

Keywords

Nephrotoxicity; poisoning; poison control center; toxicity

Introduction

Over two million poisoning exposures are reported to U.S. poison control centers annually.¹ Poisoning exposures can result in serious organ toxicity, including kidney injury. One of the more severe forms of renal injury, acute kidney injury (AKI), has been associated with adverse health outcomes, such as increased hospitalizations and extended hospital stays as well as increased mortality^{2,3} and progression to end-stage renal failure.⁴ Given the dire consequences that may occur with renal injury, identification of indicators associated with more serious kidney complications may assist health professionals to develop strategies to better manage these patients.

The use of the National Poison Data System (NPDS) to investigate patterns of kidney complications in humans is ideal due to the wide array of substances and doses of exposure documented. Managed by the American Association of Poison Control Centers (AAPCC), the NPDS collects information on drug and substance exposures reported to participating poison control centers. The comprehensive surveillance system contains more than 50 million human exposures dating as far back as 1985.⁵ Published literature on toxic exposure associated renal injury typically consists of case reports, case series, or studies limited to a single substance or class of substances.^{6–11} As national data for reported poisonings, we thought the NPDS would be a source to identify the drugs and patient characteristics associated with kidney complications given the NPDS section on “renal effects.” Utilizing the pre-defined variables that were available, we aimed to investigate the demographic and substance exposure characteristics associated with indicators for serious kidney complications (ISKC) in the NPDS.

Methods

We conducted a retrospective, case-control study of the NPDS on human exposures between 2001 and 2007 (see DISCLAIMER). Reported exposures are recorded in the NPDS and documented by Specialists in Poison Information (SPIs). Information collected includes: exposure demographics, route of exposure, clinical effects, antidotes/therapies used, and exposure scenarios. The study was reviewed and approved by the University of New Mexico Health Science Center Human Research Review Committee.

For our study, cases and controls were derived from subjects whom the NPDS had designated as having related “renal effects” which included presence of at least one or more of the following binary variables: 1) increased creatinine; 2) hematuria; 3) hemoglobinuria/myoglobinuria; 4) oliguria/anuria; 5) oxalate crystals; 6) polyuria; 7) renal failure; 8) urine color change; 9) urinary incontinence; and 10) urinary retention (definition for each variable is provided in Appendix A). Among the variables designated as “renal effects,” those considered to be ISKC include “increased creatinine,” “oliguria/anuria,” “renal failure.” ISKC is the most appropriate term for our study and is not meant to be synonymous with AKI because the NPDS does not regularly ascertain serum creatinine, duration of dialysis, and length of hospitalization. Controls were subjects who were “at risk” for the outcome, who did not have ISKC; defined as those with “renal effects” but did not have increased creatinine, nor anuria/oliguria, nor renal failure.

We utilized other variables defined by the NPDS including: sex, age, total number of substances involved, agent(s) of exposure, acuity of exposure, intentionality of exposure, healthcare facility level of care, provision of hemodialysis or hemofiltration, and medical outcome. Subjects less than 20 years of age were classified as pediatric. This cut-off was chosen to match age categories used by the AAPCC in their annual reports.^{1,12–17}

For the evaluation of drug exposures and poisonings, we were limited to the categories utilized by the NPDS. AAPCC used Poisindex® (Micromedex, Denver, CO) to catalog call information. If the substance of exposure did not have a Poisindex® code, then an appropriate AAPCC Generic Category was selected. For substance-specific analyses, cases were restricted to those involving single substances or single entity pharmaceutical preparations. We did not include cases involving multiple substance exposure or combination drugs because it would not have been possible to associate any one agent to ISKC or exclude the possibility of drug interactions.

Single substance exposures were reviewed and grouped *a priori* based on potential to cause nephrotoxic injury by our study team--a nephrology PharmD (AMV), a Nephrologist (CSW), and the Medical Director for the New Mexico Poison and Drug Information Center (SAS). Exposure agents were re-classified by the authors (AMV, CSW, SAS) into larger groups in order to manage the statistical issues related to multiple comparisons. All reviewed the drugs independently, discussed and agreed on the classification of substances into the following drug categories: acetaminophen, antineoplastics, cardiac drugs, nonsteroidal anti-inflammatories (NSAIDs), lithium, renin angiotensin aldosterone system (RAAS) inhibitors, and salicylates. Remaining substances of exposures for the logistic regression analyses were amalgamated into the following categories (examples): household and environmental substances that were likely nephrotoxic (heavy metals, ethylene glycol, and other glycols); household and environmental substances that were likely non-nephrotoxic (cosmetics, plants, miscellaneous vitamins and supplements, alcohols, etc.); medications that were likely non-nephrotoxic (anticholinergics, antihistamines, antipsychotics, anxiolytics/sedatives/hypnotics, phenazopyridine, etc.); and bites/stings. Nephrotoxic agents were defined as drugs known to cause direct toxicity to kidney

parenchyma. Drugs without known direct kidney parenchymal toxicity were not classified as nephrotoxic. See Appendix B for a complete listing of the specific items under each heading.

Utilizing the above data, we determined the association between ISKC and subject demographics, exposure characteristics, and drugs/substances. Summary statistics were used to describe exposure demographics and outcomes. Univariate and multivariate logistic regression analyses were conducted to identify factors associated with ISKC and explore the relationship between these factors. The multivariable analysis was conducted using stepwise variable selection. Cases with missing data in any of the adjustment variables were excluded from the analysis. All analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) and/or PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA). Significance thresholds were set at $p < 0.05$.

Results

EPIDEMIOLOGY

There are differences in the characterization of all exposures and those that were classified as having a “renal effect” in the NPDS. In the seven-year span of our study, there were approximately 16.8 million exposures reported to the NPDS (table 1, figure 1). Of all cases reported to the NPDS, there was a balanced gender distribution with the majority of reports involving children (65.2%) compared to adults. The majority of reports pertained to acute exposures (91.6%) that were unintentional (84.2%). There was no substantial need for health care facility admissions or mortality (<1%). In that same period of time, those classified with experiencing renal effects, our group of interest, accounted for 0.17% (N=28,645) of all who were reported to the system.

Among those with renal effects, the exposures involved 51,682 substances, with individuals exposed to a range of 1 to 21 substances with 57.4% (N=16,444) of cases involving single substances. The reports categorized with renal effects tended to differ from all exposures. The reported exposures with renal effects occurred more often in males (56.2%) compared to females; adults (76%) compared to children, and were more likely to be intentional (59.5%) compared to unintended exposures. Compared to all cases, reports with renal effects had a higher proportion of acute on chronic exposures (17.7% [renal effect] and 5.6% [all]) and chronic exposures (12.4% [renal effects] and 1.8% [all]). (See table 1 for definitions of acute on chronic exposures and chronic exposures.) Furthermore, those classified as having renal effects were more likely to be admitted to an intensive care unit (57.4% [renal effects] and 3.3% [all]) and to have a higher proportion of deaths (8.8% [renal effects] and <0.1% [all]) (table 1).

ISKC and SINGLE SUBSTANCE EXPOSURES

For our study, we restricted the analysis to those with renal effects and single substance exposures. We did not see any notable bias in restricting single substance exposures and found them to be similar to those with documented related renal effects (table 1). Among the three categorical variables used to define ISKC, the most common was elevated serum creatinine in 70.6%, renal failure was indicated in 35.2%, oliguria/anuria was coded in 26.6%. In the NPDS, a report coded with oliguria/anuria could also have been coded with elevated serum creatinine and renal failure as well, but not all patients with serum creatinine elevation would have been coded with oliguria/anuria.

Of the 16,444 subjects with single substances exposures and renal effects, there were 9,074 cases with reported ISKC (55.2%). Compared to 7,370 controls without ISKC, cases with ISKC tended to be males (54.6% [controls] versus 60.3% [cases with ISKC], $p < 0.001$), be

adults (55.6% [controls] versus 86.1% [cases with ISKC], $p<0.001$), and be reported as intentional exposures (35.6% [controls] versus 55.2% [cases with ISKC], $p<0.001$). More importantly, cases with ISKC were linked to higher rates of health care utilization such as critical care unit admission (24.5% [controls] and 69.7% [cases with ISKC], $p<0.001$). Furthermore, cases with ISKC had higher rates of reported hemodialysis or hemofiltration 27.7% (N=2,517) than controls, 2.1% (N=155), $p<0.001$ and deaths at 10.9% (N=990), compared to controls, 0.8% (N=60), $p<0.001$.

Of the 20 most common single substance exposures with renal effects, the rates of ISKC associated with each agent or category are presented in table 2. Among the top five drug classes of ISKC, we observed that cardiac drugs (98.6%) were associated with the highest proportion of ISKC, followed by acetaminophen (90.4%), salicylates (87.6%), lithium (87.3%), and ethylene glycol (85.4%). For cardiac drugs, the majority of the association was related to the component of ISKC related to elevated creatinine (77.5% of ISKC). Of the types of cardiac drugs, 493 of the 504 subjects in the category of “renal effects” were utilizing a cardiac glycoside. The substances that had a lower prevalence of ISKC’s were anxiolytics/sedative/hypnotics (36.0%), antihistamines (21.8%), anticholinergics (15.8%), diuretics (3.9%), and phenazopyridine (2.5%).

Of the three categorical variables used to define ISKC, presence of increased serum creatinine was the most reported variable for each of the 20 most common single substance exposures with renal effects, except for antihistamines, anticholinergics, and diuretics. For these substances, the most reported variable related to ISKC was oliguria/anuria, which is a well-known adverse effect associated with these classes of substance. The highest rate of death (26.0%) among individuals who experienced ISKC was observed with acetaminophen exposures.

UNIVARIABLE AND MULTIVARIABLE ASSOCIATION ANALYSIS

In the analysis of individual risk factors, we identified demographic and exposure characteristics that were associated with ISKC, demonstrated in Table 3. ISKC was associated with female gender having a lower risk compared to males (OR=0.80; 95% CI=0.75–0.85; $p<0.001$). Age was associated with risk for ISKCs. Compared with the referent group of ages 20 to 44 years, pediatric patients had a lower risk of ISKCs (OR=0.23, 95% CI=0.21–0.25; $p<0.001$) with older age groups being at higher risk for ISKCs (i.e. those in age group 45 to 64 years had a 56% increase in risk of ISKC (OR=1.56; 95% CI=1.43–1.70; $p<0.001$); 65 to 74 years a 74% increase in risk of ISKC (OR 1.74; 95% CI=1.50–20.3; $p<0.001$); >75 years a 69% increase in risk of ISKC (OR 1.69; 95% CI=1.47–1.96; $p<0.001$)). Furthermore, compared to unintentional exposures, those that were intentional had a 2.65-fold increase in risk for ISKC (95% CI=2.48–2.83; $p<0.001$).

In the categories of substances that were ingested, the referent category was household/environmental agent likely non-nephrotoxic. Included in this category were ingestion of cosmetics, paints, dyes, crayons, toys, and non-toxic plants. Consistent with the groupings, household/environmental substances considered likely nephrotoxic (i.e. such items included: ethylene glycol, heavy/toxic metals, and other glycols) were associated with a 4.65 (95% CI=4.02–5.38; $p<0.001$) increased risk for ISKC. This suggested that the groupings agreed upon by the study team appeared to be valid and robust. Assessing the a priori nephrotoxic medications, we found that acetaminophen, antineoplastics, NSAIDS, salicylates, and lithium were each associated with a several fold increase in risk of ISKC over the referent category of household/environmental agent likely non-nephrotoxic ($p<0.001$, table 3). Of interest, despite the known hemodynamic effects of RAAS inhibitors causing an increase in creatinine, they were not a significant risk factor for ISKC in our analysis. Cardiac drugs (composed primarily of cardiac glycosides) were identified to be

highly associated with ISKC (OR = 68.4; 95% CI 32.4–144.8; $p < 0.001$). Considering that cardiac drugs were associated with the highest rates of ISKC we further characterized these exposures. As mentioned earlier, the cardiac drugs consisted primarily of cardiac glycosides (97.4%, $N=493/506$) with a majority of exposures occurring in the >75 (57.3%, $N=290/506$) and 65–74 (22.3%, 113/506) years age groups.

Since all variables tested in the univariate analysis were statistically significant, these same variables, gender, age category, intentionality of exposure, and agent of exposure, were used in the multivariate logistic regression analysis along with the interaction between gender and age category. Due to missing variables, 14,417 cases were included in the analysis. All identified variables, gender, age category, intentionality of exposure, agent of exposure and the interaction between gender and age category, significantly contributed to the multivariate model ($p < 0.01$) (data not shown). The adjusted odds ratios (aOR) for ISKC, using the multivariate model, based on agent of exposure are shown in figure 2. The aOR for ISKC with likely nephrotoxic household and environmental substances (ethylene glycol, heavy/toxic metals, and other glycols) was 3.62 (95% CI 3.05–4.30; $p < 0.001$) compared to the reference group of unlikely nephrotoxic household and environmental substances (cosmetics, paints, dyes, crayons etc.) Known nephrotoxic drugs such as NSAIDs (aOR 4.27; 95% CI 3.31–5.50; $p < 0.001$), salicylates (aOR 5.58; 95% CI 4.06–7.67; $p < 0.001$), antineoplastics (aOR 5.80; 95% CI 2.84–11.82; $p < 0.001$), and lithium (aOR 7.82 (95% CI 6.25–9.78; $p < 0.001$) were associated with higher odds ratios for ISKC compared to the reference group of unlikely nephrotoxic household and environmental substances. Acetaminophen was associated with an aOR=8.08 (95% CI 6.32–10.34; $p < 0.001$) and cardiac drugs with an aOR= 60.48 (95% CI 28.31–129.21; $p < 0.001$) odds for ISKC, while RAAS inhibitors were not associated with an increased adjusted odds for serious renal complications, aOR= 0.69 (95% CI 0.46–1.02; $p < 0.001$).

EXPLORATION OF ASSOCIATION WITHIN GROUPS

Regardless of reported gender, we observed that the risk of ISKC was higher with each age group older than the referent of 20–44 years (figure 3, panel A). Pediatric patients (<20 years) had a lower rate of reported ISKC compared to older age groups. Females in the 20–44 (aOR=0.88; 95% CI 0.84–0.93; $p < 0.001$) and 45–64 (aOR=0.81; 95% CI 0.75–0.88; $p < 0.001$) year age groups were less likely than their male counterparts to develop serious renal complications (figure 3, panel B).

Discussion

We found that data from the NPDS offered unique insight into the epidemiology of subjects and types of exposures that associate with ISKC. The NPDS is a valuable source of data for toxic exposures reported to poison control centers nationwide. In the NPDS, the reported exposures that were coded in the NPDS subcategory of “renal effects” represent a rare group of exposures (0.17%). Yet, the cases with “renal effects” were more likely to be associated with adverse outcomes, particularly cases with ISKC. The subjects with ISKC had higher rates of intensive care unit admission and death compared to the respective rates of all reported exposures. Due to the high rate of adverse outcomes linked to ISKC, we characterized subject characteristics and patterns of exposures that were associated with ISKC. We found that substances that were *a priori* considered nephrotoxic did associate with ISKC as will be discussed in further detail below. Furthermore, the multivariate analysis of the NPDS, ISKC was associated with age, gender, and intentionality of exposure.

The NPDS has been utilized for other outcome studies to understand patterns of poisoning, drug exposure and overdose. The NPDS has been utilized in conjunction with electronic surveillance methods to monitor toxicological outbreaks.^{18–20} In addition to monitoring for

previously unreported adverse substance effects,^{21,22} the NPDS database has been used to demonstrate and develop dose-response curves for diphenhydramine,²³ clonidine,²⁴ and tilimicosin,²⁵ to help establish triage and healthcare facility referral criteria,^{23,26} and to anticipate dose-related clinical effects. Consistent with other studies to determine the association of specific substances and reported effects, we restricted our analysis to cases involving single substances or single entity pharmaceuticals in order to draw a more direct association between the agent of exposure and serious renal complications. After adjusting for gender, age category, intentionality of exposure, agent of exposure and the interaction between gender and age category, there was a strong association between known nephrotoxins and ISKC.

Information contained in databases such as the NPDS may be helpful in further elucidating important predictors of renal injury or impairment. The associations between known nephrotoxins and ISKC were consistent with reports in the literature. Our study of the NPDS identified patterns of reported kidney complications from ingestions and drug overdoses, especially with over-the-counter analgesic medications. In 1996, D'Agati's identified conflicting reports on the ability of aspirin to cause acute or chronic kidney injury in animal and human studies; however, acute aspirin intoxication was noted to frequently cause acute renal failure.²⁷ Despite the dearth of literature regarding salicylate nephrotoxicity since this 1996 report, we observed a strong association between salicylate compound exposure to ISKC in our cohort from 2001 to 2007. Known to cause renal injury when taken in therapeutic doses^{28–30} and overdoses,^{31–34} NSAIDs were strongly associated with ISKC. Furthermore, acetaminophen, a drug well known for its hepatotoxicity, also demonstrated a strong association with ISKC. The acute nephrotoxicity of acetaminophen has been described in a number of case reports and series,^{10,11,35–39} animal models support direct nephrotoxicity by the metabolites of this compound.^{40–42} However, acetaminophen may also have specific effects on renal physiology.⁴³ Although an association study cannot identify a cause and effect relationship, the associations we identify are consistent with other reports in the literature and support the use of the NPDS to assess the potential for adverse kidney outcomes.

We had expected to observe a positive association between RAAS inhibitors and ISKC, however our results suggest that these substances were not associated with renal complications. The most common manifestation of RAAS inhibitor overdose reported in case reports and series is hypotension.^{6,44–46} Systemic hypotension in addition to efferent arteriole vasodilation are the likely mechanisms by which RAAS inhibitors cause renal injury. Lucas et al. described a transient rise in serum creatinine concentration in 6 of 33 patients (18.2%) treated for angiotensin converting enzyme inhibitor overdose at their institution.⁴⁶ RAAS inhibitor induced serious renal complications could easily be prevented with proper fluid and blood pressure management, which potentially explains the absence of observed ISKC with RAAS inhibitor toxic exposure. It has been reported that adverse effects associated with RAAS inhibitor overdose are generally mild.^{46,47} Alternatively, this counterintuitive finding may be due to unrecognized misclassification, bias, or cohort effect in the NPDS for this class of drug. The observed association of RAAS inhibitors and lower risk of ISKC may be clarified by independent validation in another cohort to either support or refute our observations.

This analysis of the NPDS demonstrated older age was associated with ISKC, consistent with known observations that older age increases the risk of acute kidney injury.^{48–50} Furthermore, within each age category, we identified differences in reports of ISKC that demonstrated differential susceptibility to kidney injury by gender. Although it is unclear why there may be differences by gender within each strata of age, we speculate that the

associated differences by gender are potentially related gender specific characteristics such as preferences for particular agents of exposure and differences in ingested dose.^{51,52}

From the above, we see that the data in the NPDS identifies strong relationships between demographic and characteristics of ingested exposures and abnormal kidney functional status. We note that it is also important to have a mechanistic understanding of statistically significant relationships found in our analysis. Above, we found relationships between known nephrotoxins and ISKC. However not all relationships indicate nephrotoxic injury as illustrated by the case of our category of cardiac related drugs—primarily comprised of cardiac glycosides. It is anticipated that complications with cardiac glycosides to be highly linked to kidney impairment. Rather than a dosing error of a cardiac glycoside causing kidney impairment, it is apparent that subjects with pre-existing kidney impairment would have further complications with cardiac glycosides given that the majority of reported incidents for these drugs were in the elderly population, who are more likely to have impaired kidney function.^{48–50} Despite the usefulness of the NPDS, it is still important to emphasize the need for sound interpretations of the relationships based on underlying mechanisms and pathophysiology.

The NPDS data from 2001–2007 gives some insight into the patterns of exposures associated with recorded variables indicating kidney dysfunction. Analysis of the subsequent years of NPDS data can be used to independently validate these findings. The associations identified in the current analysis are highly significant and the addition of more data would not considerably augment the findings of the study.

The NPDS has limitations (see DISCLAIMER) sufficient for us to clarify that the variables used are “indicators” of kidney impairment, since serum creatinine level and hospital records are not verified. We are also limited to the effect codes that have been pre-defined in the database. We acknowledge that clinical effect codes are voluntary fields and shown to be variably completed.⁵³ As mentioned earlier, the effect codes are coded in a binary manner and without regard to timing in relation to the exposure or magnitude of the effect. Although it is possible to crudely identify indicators of kidney complications and possible kidney impairment, it is not to the level of detail found in the RIFLE (Risk, Injury, Failure, Loss, End stage) or AKIN (Acute Kidney Injury Network) criteria for AKI.^{54,55} Despite our conservative interpretation of the data, our approach in utilizing the NPDS demonstrated that the amalgamated categories as ISKC identified relationships between nephrotoxic drugs and kidney impairment or injury as well as drug exposures that are further complicated with kidney impairment.

We acknowledge that there are other limitations and weaknesses of a retrospective analysis of NPDS. Given the retrospective analysis and the voluntary nature of the reporting it is difficult for us to rule out other causes related ISKC such as dehydration or sepsis. Poisoning is not a reportable condition and thus subject to selection bias and may not necessarily include all exposures that present to emergency departments or other exposures where a poison call center is not consulted. Although studies regarding the accuracy of NPDS data show that the NPDS is consistent in capturing relevant outcomes, the NPDS but may underestimate the true incidence of exposures.⁵⁶ Additionally, the data is largely collected from secondhand reports resulting in unknown or missing data and potentially recall bias. Further, we acknowledge that there are domains of our analysis that demonstrate clear selection bias. For example, in order for ISKC to be identified subjects must be in a health care facility to have a serum creatinine drawn, oliguria/anuria identified, or renal failure diagnosed.

The data obtained from the NPDS represents a broad population-based sample of poisonings that are reported to AAPCC centers. However, the sampling of the population might be biased due to the differences in utilization of poison control centers. Litovitz et al. identified that poison center utilization was decreased among African-Americans, populations with limited English, and long-distances from the poison center.⁵⁷ Despite the above limitation, our study demonstrates the novel use of the NPDS to identify patterns of ISKC to poison control centers across the United States. Though this NPDS analysis may be of value, the study only serves as a hypothesis generating function to support further studies with rigorous data collection and ascertainment of short and long-term outcomes for patients reported to have a kidney injury.

Conclusions

We found that data from the NPDS reliably identified *a priori* associations between known nephrotoxins and indicator variables for kidney dysfunction. In addition, the database reliably identified groups that are known to be at risk for kidney impairment. The hypothesis generating analysis found that toxic exposures within the NPDS pre-defined category of “renal effects” were associated with increased morbidity and mortality compared to all other exposures especially among those whom we had classified with ISKC. Similar analyses may allow validation of our findings regarding potentially nephrotoxic exposures. The NPDS database offers a unique perspective on nephrotoxic exposures and the opportunity to better characterize the demographic, clinical effects, and management of these exposures. We hope that the hypotheses generated from this study of the NPDS will raise awareness of the possible risk factors and complications associated with ISKC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Flow diagram of exposures documented in NPDS (2001–2007) depicting how indicators of kidney complications (ISKC) “Controls” and “Cases” were identified.

Figure 2.

Adjusted odds ratio for indicators of serious kidney complications (ISKC) based on substance of exposure. Referent group Household/Environmental Agents Non-Nephrotoxic.

Figure 3.

Adjusted odds ratio for indicators of serious kidney complications (ISKC) based on age (Panel A: Referent group are subjects 20–44 years of age.) and differences on risk for ISKC by gender within each age category (Panel B).

Table 1
Demographic information and outcome of individuals involved in toxic exposures documented in NPDS (2001–2007)

Parameters	All Exposures ^{12–17,58} N=16,791,993	Exposures with renal effects N=28,645	Single substance exposures with renal effects N=16,444	Single substance exposures with renal effects with indicators of serious kidney complications (ISKC) N=9,074
Gender				
	Male	16,090 (56.2%)	9,492 (57.7%)	5468 (60.3%)
	Female	8,564,146 (51.0%)	6,917 (42.1%)	3591 (39.6%)
Mean Age ± SD		37.7 ± 20.4	37.7 ± 22.4	44.3 ± 20.0
	Adult	5,745,036 (34.2%)	21,721 (76%)	7811 (86.1%)
	Pediatric	10,953,732 (65.2%)	5,681 (19.8%)	971 (10.7%)
Acuity of exposure to agent				
	Acute *	15,385,754 (91.6%)	10,404 (63.3%)	5109 (56.3%)
	Acute on chronic **	935,248 (5.6%)	2,254 (13.7%)	1207 (13.3%)
	Chronic ***	319,054 (1.9%)	2,435 (14.8%)	1727 (19.0%)
Intentionality of exposure				
	Intentional	2,063,206 (12.3%)	7,631 (46.4%)	5009 (55.2%)
	Unintentional	14,132,995 (84.2%)	9762 (34.1%)	3152 (34.7%)
Level of Care				
	Admitted to ICU	549,896 (3.3%)	16,440 (57.4%)	6323 (69.7%)
	Admitted to non-ICU	303,922 (1.8%)	3,425 (12.0%)	1387 (15.3%)
	Admitted to psychiatric facility	307,484 (1.8%)	743 (2.6%)	137 (1.5%)
Death				
		8,245 (<0.1%)	1,050 (6.4%)	990 (10.9%)

* Acute = A single, repeated or continuous exposure occurring over a period of eight hours or less

** Acute on chronic = A single exposure that was preceded by a continuous, repeated, or intermittent exposure occurring over a period exceeding eight hours

*** Chronic = A continuous, repeated, or intermittent exposure to the same substance lasting longer than eight hours

Table 2

Twenty most common single substance exposures with renal effects and incidence of indicators of serious kidney complications (ISKC) along with rates of ISKC components, renal replacement therapy, and death among those who experienced ISKC

Agent	Incidence of ISKC	SCr ⁺	Oliguria/anuria	Renal Failure	HD/HF ⁺⁺	Death
Cardiac Drugs ⁺⁺⁺ (N=506)	98.6%	77.5%	8.9%	37.2%	7.5%	6.5%
Acetaminophen (N=946)	90.4%	73.2%	19.3%	36.7%	19.1%	26.0%
Salicylates (N=450)	87.6%	71.1%	18.0%	14.9%	26.7%	6.7%
Lithium (N=995)	87.3%	75.5%	10.6%	18.2%	37.4%	1.9%
Ethylene Glycol (N=1,484)	85.4%	66.8%	32.8%	42.0%	74.8%	8.5%
Ibuprofen (N=324)	81.8%	68.8%	8.0%	14.8%	3.7%	1.2%
Alcohols (excluding ethylene glycol) (N=775)	69.3%	56.6%	10.2%	13.0%	14.5%	5.8%
Stimulants (N=353)	67.4%	48.4%	19.0%	25.2%	14.4%	15.0%
Opiate Agonists (N=620)	64.0%	46.8%	15.8%	22.1%	10.6%	10.5%
Amphetamines (N=488)	57.0%	35.2%	23.2%	17.4%	10.2%	8.0%
Miscellaneous drugs (N=1,120)	56.8%	35.4%	11.7%	24.2%	8.9%	5.2%
Miscellaneous (excludes drugs) (N=891)	53.1%	30.9%	14.4%	24.2%	12.3%	7.5%
Anti-infectives (N=453)	52.3%	26.7%	10.3%	22.7%	8.4%	1.5%
Anticonvulsants (N=284)	44.0%	22.9%	21.5%	9.9%	4.9%	3.9%
Antipsychotics (N=355)	39.4%	20.3%	15.2%	10.1%	4.2%	2.5%
Anxiolytics/Sedatives/Hypnotics (N=286)	36.0%	19.9%	17.8%	9.8%	6.6%	2.8%
Antihistamine (N=473)	21.8%	10.4%	11.8%	4.0%	2.3%	1.5%
Anticholinergics (N=341)	15.8%	2.6%	12.6%	0.9%	0.3%	0.3%
Diuretics (N=1,296)	3.9%	1.1%	2.3%	0.7%	0.1%	0%
Phenazopyridine (N=511)	2.5%	2.5%	0.2%	1.1%	0.6%	0%

⁺ SCr = serum creatinine increase

⁺⁺ HD/HF = hemodialysis/hemofiltration

⁺⁺⁺ Cardiac drugs = antiarrhythmics and cardiac glycosides; category excludes antihypertensives, diuretics, and RAAS inhibitors

Table 3

Univariate odds ratio for indicators of serious kidney complications among single substance exposures with renal effects (N=16,444)

Factor		No ISKC “Controls” (N)	ISKC “Cases” (N)	Univariate Odds Ratio (95% CI)
Gender				
	Male (N=9,473)	4,024	5,468	1.00 (reference)
	Female (N=6,917)	3,326	3,591	0.80 (0.75–0.85)
Age Category				
	0–19 (N=3,718)	2,751	967	0.23 (0.21–0.25)
	20–44 (N=5,879)	2,341	3,538	1.00 (reference)
	45–64 (N=4,005)	1,193	2,812	1.56 (1.43–1.70)
	65–74 (N=974)	268	706	1.74 (1.50–2.03)
	>75 (N=1,050)	295	755	1.69 (1.47–1.96)
Intentionality of exposure				
	Unintentional (N=7,631)	2,622	5,009	1.00 (reference)
	Intentional (N=7,517)	4,365	3,152	2.65 (2.48–2.83)
Substance of exposure				
	Household/environmental agents; likely nephrotoxic (N=1,676)	287	1,389	4.65 (4.02–5.38)
	Household/environmental agents; likely non-nephrotoxic (N=2,950)	1,445	1,505	1.00 (reference)
	Medications; likely non-nephrotoxic (N=7,876)	4,851	3,025	0.70 (0.55–0.65)
	Bites/stings (N=364)	280	84	0.29 (0.22–0.37)
	Acetaminophen (N=946)	91	855	9.02 (7.18–11.33)
	Antineoplastics (N=65)	10	55	5.28 (2.68–10.40)
	All NSAIDs (N=467)	113	354	3.01 (2.41–3.76)
	Cardiac Drugs (N=506)	7	499	68.44 (32.35–144.82)
	Lithium (N=995)	126	869	6.62 (5.42–8.09)
	RAAS Inhibitors (N=149)	104	45	0.42 (0.29–0.59)
	Salicylates (N=450)	56	394	6.76 (5.06–9.02)