Adverse Drug Effects In New York State Angiocardiography Hospitalizations: 1996-2010

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Citation

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Abstract

Angiocardiography hospitalizations (n=1,971,571) in New York State were examined for adverse drug effects between 1996 and 2010 focusing particularly on radiocontrast material (RCM) related hypersensitivity manifestations. Using the E code E947.8 (adverse drug effect from radiocontrast) and coding for other anaphylaxis (ICD9 995.0), allergic urticarial (ICD9 708.0), angioedema (ICD9 995.1), laryngospasm (ICD9 478.6) or laryngeal edema (ICD9 478.75) , an overall immediate hypersensitivity rate of 16.04x10-5 was found. Logistic regression modeling found that these immediate hypersensitivity manifestations were most strongly predicted by coding for E947.8 (odds ratio 501: 95%CI 433-580) followed by adverse coding to anti-infective, analgesic/anti-rheumatic, anti hypertension or cardiovascular drugs(odds ratio of any of these 84.91: 95% CI 69-104). There was an overall increase in the proportion of hospitalizations coding for these immediate hypersensitivity manifestations over the study period(binomial regression for time effect p<0.0001). Multivariate modeling showed not only a year effect but also a significant predictor effect from younger age, longer length of stay and female gender. Although a history of allergy to food, insect, latex, RCM or other substances were also multivariate predictors, asthma was not. Over a period of time when non-ionic RCM has predominated, the inpatient rate of RCM associated immediate hypersensitivity reactions associated with cardiac angiography has continued to exceed the combined rate of other common drug associated immediate hypersensitivity reactions, overall by more than 2 fold.

Introduction

Since the 1990's non-ionic contrast materials have essentially replaced the older ionic contrast materials for radiographic studies(1,2). While the incidence of hypersensitivity reactions is known to be lower with these newer contrast agents, the expanded use of contrast studies has led to more exposure, especially in hospitalized and emergency room patients. In New York State, like the entire United States(3), coronary artery angiograms are frequently performed as pre-interventional assessments of remediable disease. As acute hospitalizations in New York State are well documented with the SPARCS administrative database, examination of adverse effects due to medication and radiocontrast material (RCM) associated with angiography can potentially be characterized over more recent years.

Methods

De-identified in-patient data was obtained from the New York State Department of Health Statewide Planning and Research Cooperative System (SPARCS) database(4) for 1996 through 2010. The database has been previously described and utilized in studies examining disease states and hospital practice trends(5,6). Each SPARCS patient record contains data fields that include principal and non-principal diagnostic fields, accommodation and ancillary charges, procedure codes, race, age, gender, and ethnicity information, hospital characteristics, expected reimbursement, total charges, length of stay, admission and disposition status. This study was approved by the institutional research board of New York Downtown Hospital.

Admissions associated with cardiac or peripheral vascular angiography were identified using the procedural code ICD-9 code 88.5 (angiocardiography). To avoid admissions where additional contrast was potentially administered, admissions with the CT associated procedural ICD9 codes for CT abdomen (88.01) CT head (87.03) CT heart (87.41) CT kidney (87.71) and CT thorax (87.41) were excluded. Admissions with potentially non-cardiac arteriography (88.4) and contrast associated urologic studies such as intravenous pyelogram (87.73), retrograde pyelogram (87.74), percutaneous pyelogram (87.75), retrograde cystourethrogram (87.76), other cystogram (87.77) and ileal conduitogram (87.78) were likewise excluded. Adverse effect codes(E codes) for various drugs were identified and included anti-infectives (E930.* and E931.*) and anti-rheumatic agents antipyretics and analgesics (E935.*), other anti-hypertensive agents (code E942.6), other unspecified cardiovascular agents (E942.9) and other drugs and medicinal substances causing adverse effects in therapeutic use(contrast media used for diagnostic x-ray procedures; diagnostic agents and kits)(E947.8). Admissions where E947.8 was present-on-admission were also excluded as these admission may have been ambulatory cases admitted only because an adverse reaction to radiocontrast material and thus not be representative of typical inpatient angiocardiography admissions.

Several diagnoses were also identified for being an on admission condition, including hypertension (HTN) (ICD9 401.*), asthma (ICD9 493.*), chronic kidney disease (CKD) (ICD9 585.*), and diabetes mellitus (DM) (ICD9 250.*). The SPARCS databases include a “present-on-admission” status for all diagnoses listed(7). Thus a clinical state which is present but coded as not “present on admission” occurred after admission but was not present at the time of admission.

Diagnoses/conditions which could possibly be an immediate hypersensitivity manifestation of a drug adverse effect were identified only if the condition was not present-on-admission and included the following; other anaphylaxis (ICD9 995.0), allergic urticarial (ICD9 708.0), angioedema(ICD9 995.1), larygospasm (ICD9 478.6) or laryngeal edema (ICD9 478.75). Other conditions not present-on-admission that could potentially be a manifestation of a radiocontrast adverse effect were identified, and included nephritis and nephropathy, not specified as acute or chronic with other specified pathological lesion in kidney (ICD9 583.89), seizures (ICD9 780.39), acute kidney failure(ICD9 584.*), dermatitis due to drugs (ICD9 693.0/693.8/693.9), dyspnea (ICD9 786.09), tachycardia (ICD9 427.89), iatrogenic hypotension (ICD9 458.29), pulmonary edema (ICD9 506.1), allergy unspecified(not elsewhere classified)(ICD9-995.3), fever unspecified (ICD9 780.60), wheezing (ICD9 786.07), flushing (ICD9 782.62), and bronchospasm (ICD9 519.11). V codes were also identified specifically for personal history of allergy, other than to medicinal agents, presenting hazards to health (V15.0*) separating out V15.08 (allergy to radiographic dye) from the other personal allergy histories(these include foods, insects/arachnids and other allergy). The major diagnostic category of disease (MDC)(8) was also identified for the hospitalizations. Age, gender and hospital length stay were also examined.

Data analysis was performed using SPSS for Windows(Version 13, SPSS Inc, Chicago, IL, USA) for all analyses except negative binomial regression. Negative binomial regression was performed using SAS for Windows version 9.1 (SAS Institute, Cary, NC,USA) to analyze trends of adverse effects using the GENMOD procedure taking into account the total cohort as the offset variable(9) as previously described(10). Logistic regression was performed to examine significant multivariate associations. Predictor effects examined included demographic variables (age, , age, sex and year of

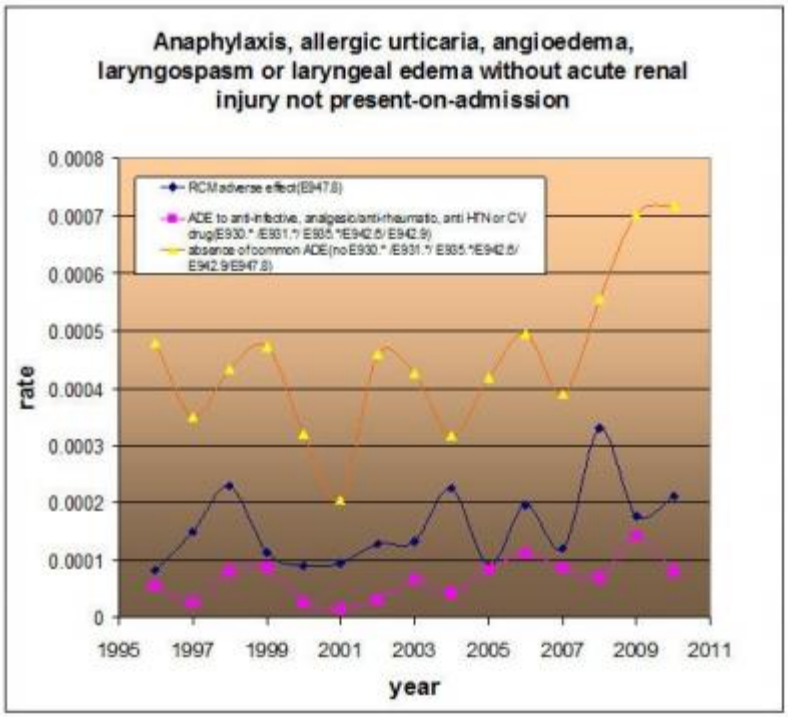
study), as well as certain relevant co-morbidities, clinical signs and symptoms, certain V codes, length of stay ,the top six MDC categories, and categories of adverse drug effects(E codes). Stepwise forward selection was employed.

Results

Excluding 2,570 hospitalizations that on admission, had an adverse effect due to other drugs and medicinal substances causing adverse effects in therapeutic use (contrast media used for diagnostic x-ray procedures; diagnostic agents and kits)(E947.8), there were 1,971,571 hospitalizations which had procedural ICD-9 code 88.5(angiocardiography) without having had the other identifiable radiological procedures aforementioned as exclusions. The per year number of hospitalizations ranged from 108,856 in 1996 to 143,078 in 2005. Four thousand two hundred and sixty eight (.2%) of these hospitalizations had a code of E947.8 that was not present-on-admission. In 1996, 124 (0 .1%) of hospitalizations had an E947.8 code. This increased to 445 (0.3%) in 2010. Of these 4268 E947.8 coding hospitalizations, 336 (7.9%) had likely immediate hypersensitivity manifestation codes (995.0/708.0/995.1/478.6/478.75). In contrast, 2,449 (57.4%) had acute renal injury codes(583.89 and 584.*) not present-on-admission. Only 16 (.4%) E947.8 admissions had both immediate hypersensitivity manifestations coding and acute renal injury codes. 420(9.8%) E947.8 admissions had not-on-admission cardiorespiratory, cutaneous, fever/seizure codes without concomitant immediate hypersensitivity or renal injury codes.
Male gender was associated with 59.5% of the hospitalizations. The race was Caucasian in 73% and African-American in 12.9% of the hospitalizations. The median length of stay was 4 days but decreased from 1996(5 days) to 2004 onward (3 days). The median age was 66 years. 83.6% of the hospitalizations were classified as MD6 (Circulatory). 4.4%. 2.5%, 1.8%, 1.3% and 1.1% of hospitalizations were MDC1 (Neurological), MDC4 (Respiratory), MDC6 (Digestive), MDC8 (Musculoskeletal) and MDC11(Kidney/Urinary) respectively. The principal diagnosis was coronary atherosclerosis (ICD9 414.0*) in 36% hospitalizations and acute myocardial infarction (ICD9 410.*) in 17.8%. Hypertension, diabetes mellitus, chronic renal insufficiency and asthma were present-on-admission in 50.7%, 28.5%, 5.6% and 4.5% of hospitalizations respectively. A personal history of allergy to food, insect latex or other but not RCM was coded in 1832 hospitalizations whereas a personal history of allergy to RCM was coded in 1326 hospitalizations.
Acute kidney injury or nephritis/nephropathy not present-on-admission increased during the study period both in admissions with a E947.9 not present-on-admission (37.9% in 1996 , 62% in 2010) and in the other(non-E947.8) admissions(2.3% in 1996, 4.2% in 2010). The rate of E947.8 associated hospitalizations that manifested anaphylaxis, allergic urticaria, angioedema, laryngospasm or laryngeal edema without acute renal injury not present on admission also increased over the study period (Figure 1) with an overall rate 16.04x10-5). There was also an increase these immediate hypersensitivity manifestations in hospitalizations that coded adverse drug effects to other classes of drugs (overall rate 6.80x10-5)as well as in hospitalizations without any of these adverse drug effects (overall rate 45.23x10-5). There was a significant year effect for immediate hypersensitivity manifestations(negative binomial regression $p<0.001$) , and there were significant between group effects between all three above groupings based on adverse effect coding significant group by time effects ($p<0.001$ for all between group comparisons). But there was no significant group by time effects.

Figure 1

Anaphylaxis, allergic urticaria, angioedema, laryngospasm or laryngeal edema without acute renal injury not present-on-admission



Strong logistic regression predictor effects for immediate hypersensitivity manifestation codes were found for E947.8, having codes for other adverse drug effects (E930.* /E931.*/ E935.*/E942.6/ E942.9), not having acute kidney injury/nephritis/nephropathy(not present-on-admission) and not having dermatitis due to drug(not present on admission). Predictor effects were also found for certain demographic factors and clinical conditions. These are shown in Table 1.

Table 1

Predictors of anaphylaxis, allergic urticaria, angioedema, laryngospasm or laryngeal edema not present-on-admission

factor	p-value	odds ratio	lower 95%CI	upper 95%CI
Renal injury or other nephritis/nephropathy not present-on-admission	0.000	0.02	0.01	0.03
Dermatitis due to drug not present-on-admission	0.000	0.06	0.03	0.12
Male gender	0.000	0.80	0.71	0.89
History of allergy to radiocontrast V15.08	0.025	3.28	1.17	9.26
Discharge year	0.000	1.04	1.03	1.06
Length of stay	0.000	1.004	1.003	1.006
Age	0.000	0.989	0.985	0.992
E947.8(radiocontrast ADE)	0.000	501	433	580
V15.0*History of allergy to latex, foods, insects and other(excluding RCM V15.08)	0.004	3.68	1.50	9.02
ADE to anti-infective, analgesic/anti-rheumatic, anti-hypertension or cardiovascular drug	0.000	84.91	69.36	103.95
MDC1(Neurologic)	0.000	1.58	1.27	1.96
Cardiorespiratory signs and symptoms not present-on-admission	0.000	1.64	1.35	1.99
Chronic renal disease	0.034	0.76	0.59	0.98

In order to more specifically identify factors relating immediate hypersensitivity reactions associated with radiocontrast, logistic regression was performed excluding hospitalizations having acute renal injury codes(not present-on-admission), and dermatitis due to drug(not present on admission). Similar associations were noted. These associations are noted in Table 2.

Table 2

Predictors of anaphylaxis, allergic urticaria, angioedema, laryngospasm or laryngeal edema not present-on-admission, excluding dermatitis due to drug and renal injury not present-on-admission

factor	p-value	odds ratio	lower 95%CI	upper 95%CI
length of stay	0.000	1.005	1.003	1.006
Age	0.000	0.988	0.984	0.991
Discharge year	0.000	1.04	1.02	1.05
Male gender	0.000	0.78	0.70	0.88
MDC1(Neurological)	0.000	1.64	1.31	2.04
MDC8(Musculoskeletal System And Connective Tissue)	0.029	1.53	1.04	2.24
V15.0* history of allergy to latex, foods, insects and other(excluding RCM V15.08)	0.003	3.86	1.57	9.49
E947.8(radiocontrast ADE)	0.000	574.3	496.7	664.1
history of allergy to radiocontrast V15.08	0.023	3.41	1.18	9.81
ADE to anti-infective, analgesic/anti-rheumatic, anti-hypertension or cardiovascular drug	0.000	101.1	81.9	124.8

Younger age, later discharge year, longer length of stay, having a neurologic MDC1, musculoskeletal MDC8 and female gender showed significant predictor effects for immediate hypersensitivity manifestation codes in both regression models, as did a history of allergy to radiocontrast allergy and a history of allergy to non-RCM items. The strongest predictors were coding for E947.8 (radiocontrast) followed by and adverse drug effect related to anti-infective, analgesic/anti-rheumatic, anti-hypertension or other cardiovascular drugs. Asthma did not have a predictor effect in either model.

In order to examine for whether there was an interaction between RCM (E947.8) and various clinical factors(generally recognized to be risk factors for RCM hypersensitivity reactions), interaction factors were created and entered into the regression model. This included RCM (E947.8) by asthma, RCM (E947.8) by history of RCM allergy, and RCM (E947.8) by history of allergy to food, insect, latex or other. None of these interaction terms were selected has having predictor effects in multivariate regression modeling.

Discussion

These data show that the rate of RCM associated immediate hypersensitivity reactions in a large cohort of angiocardiography (which in all probability consisted mostly of cardiac catheterizations) hospitalizations is very low approaching 2 per 10,000) in an era of predominantly non-ionic radiocontrast use. This is consistent with the rate of severe allergic reactions associated with non-ionic RCM reported by others(11). This suggests that reporting of RCM adverse drug effects in administrative databases focuses on more severe reactions. Although the rate associated with RCM appears to be increasing, the overall rate of immediate hypersensitivity rates is also increasing, suggesting better reporting and coding in more recent years as a possible explanation or more susceptible patients at risk for hypersensitivity reactions. The proportion of RCM ADE coding patients without any common hypersensitivity, cardiopulmonary, or renal manifestations coded was still more than 20%(data not shown) but much less than initial years. The predominant RCM adverse drug effect appears to be renal injury, especially in more recent years.

We did not observe an interaction effect between asthma and RCM associated immediate hypersensitivity reactions, now did we find any predictor effect for asthma itself. It is possible that many of 4.5% hospitalizations where asthma was present-on-admission, had prophylactic treatment directed against the risk of an RCM associated hypersensitivity reaction thus dampening this historical risk factor effect. Also since the model looked at all immediate hypersensitivity manifestations including those not associated with RCM ADE, the specific predictor effects on RCM ADE associated immediate hypersensitivity reactions may not have been detected. Speaking against this possibility is the identified predictor effect from historical RCM ADE reactions, which was significant despite the likelihood that this risk factor also would have been identified and treated with prophylactic regimens. This suggests that asthma is either not that strong of a risk factor and/or that prophylactic treatment eliminates the predictor effect of this risk factor. Asthma has been reported be associated with a 6 fold risk for RCM reactions with low osmolarity contrast media(12).

Our data confirm that younger age is a risk factor for RCM associated immediate hypersensitivity reactions. The risk of RCM associated reactions has been shown to be more in patients greater than 60 years compared to those between 20-50 years of age(13). The median age of patients in this cohort was 66 thus making the majority of patients in this cohort in the high risk age category. This is age related risk is consistent with concepts of many forms of atopy manifesting relatively more in youth(14). We have previously examined angioedema(which was strongly associated with ACE inhibitor adverse effect coding) and compared anaphylaxis, urticaria and other allergy admissions in the United States(15,16) and shown that the latter group is associated with younger age(median age for angioedema 61 versus median ages of 52, 45 and 46 for anaphylaxis, urticaria and other allergy) . This present study differed in that it did not look at hospitalizations with a principal diagnosis

(which implies on admission presentation) of allergic disease but only examined for allergic disease that developed during hospitalization(not present-on-admission).
Our findings that dermatitis due drug presenting during the hospitalization(not present on admission) is not characteristic of RCM adverse drug effects, which seem to much more strongly associated with immediate hypersensitivity coding at least in the hospital setting. It is likely that adverse drug effects due to anti-infective, analgesic/anti-rheumatic, anti-hypertension or other cardiovascular drugs, were more related to dermatitis due to drug coding, but these adverse drug effects certainly cause immediate hypersensitivity reactions as well. The V codes associated with personal allergy history had significant but weaker associations with immediate hypersensitivity reactions in multivariate modeling and due to the model design could have represented risk factors for drug reactions in general. Interestingly the risk of RCM allergy (odds ratio 3.28) and non-RCM allergy(odds ratio 3.68) found in the present study were similar in magnitude to that reported 3 and 5 fold risk(respectively) reported in the literature(12). We were unable to show an interaction effect between personal allergy histories and coding for RCM adverse drug effects. Although one could argue that this was due to a lack of increased risk in RCM associated immediate hypersensitivity reactions, it is equally plausible to hypothesize that these personal allergy histories contribute equally to RCM associated and non-RCM associated hypersensitivity reactions in this population.
In cardiac angiography hospitalizations, immediate hypersensitivity manifestations related to RCM adverse effects have been uncommon in recent years, where non-ionic contrast material is the norm. However they still are consistently more common that immediate hypersensitivity reactions due to other medications combined.

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