

Safety of Administering Furosemide During Nuclear Diuretic Renography in Patients With Sulfonamide Allergies

Yingbing Wang¹
David Z. Chow
Leonard P. Connolly
James A. Scott
Edwin L. Palmer

OBJECTIVE. We reviewed the safety of nuclear diuretic renography with furosemide in patients with sulfonamide allergies. The electronic health record was used to uncover any drug effects reported within 30 days of diuretic renograms performed between January 2009 and December 2015.

CONCLUSION. Eighty-three of 1103 (7.5%) diuretic renograms were performed on patients with sulfonamide allergies. Two instances of minor rash occurred. No serious reactions occurred. Furosemide is associated with an extremely low risk of minor reactions in patients with sulfonamide allergies.

Diuretic renography is a nuclear medicine examination performed to characterize urinary drainage patterns in patients with suspected renal or ureteral obstruction. Incomplete and delayed drainage from the collecting system despite diuresis supports a diagnosis of at least partial obstruction. Furosemide, a sulfonamide-containing drug, is the standard diuretic used for the examination, and no alternative diuretic has been widely validated. Among patients undergoing diuretic renography, reported allergies to sulfonamide antimicrobial agents are common and pose an important question about the safety of furosemide administration. Other diuretics, such as bumetanide and ethacrynic acid, are not chemically related to sulfonamide drugs and may be considered acceptable alternatives, but they are not widely available in most outpatient or inpatient formularies. Provocative maneuvers might alternatively be performed to augment diuresis; however, the efficacy of these maneuvers is uncertain, because, to our knowledge, no head-to-head comparisons with furosemide have been performed.

Adverse reactions to sulfonamide-containing drugs are estimated to occur in 3% of patients and are predominantly associated with antimicrobial agents rather than nonantimicrobial drugs [1]. Hypersensitivity reactions typically develop 7–14 days after sulfonamide exposure and most commonly are manifest as a maculopapular rash. Only 3% of reported re-

actions to sulfonamide drugs are considered to represent true hypersensitivity reactions [2]. There is no reliable skin test to exclude or confirm sulfonamide allergy.

Researchers have shown that serum-derived antisulfamethazine antibodies from allergic patients do not bind to furosemide [3], and in the single published case report of anaphylaxis associated with furosemide usage, the authors did not prove conclusively that the allergen was, in fact, chemically related to the sulfonamide moiety [4]. A large retrospective cohort study (of 969 patients who had had allergic reactions to sulfonamide antibiotics and of 19,257 patients who had not) by Strom et al. [1] showed that patients allergic to sulfonamide antibiotics were more likely than nonallergic patients to react to sulfonamide nonantibiotics (9.9% vs 1.1%). However, they also found that the rate of reaction was even greater among patients allergic to penicillin who received sulfonamide nonantibiotics (14.2%). Because penicillins do not have a sulfonamide moiety, the higher rate of sulfonamide cross-reactivity is hypothesized to be attributed to a greater underlying predisposition to allergic reactions among patients allergic to sulfonamide antibiotics.

Although the likelihood of a clinically important adverse reaction to furosemide in the setting of minor sulfonamide allergies would thus appear unlikely, there are presently no clear guidelines from the Society of Nuclear Medicine and Molecular Imaging or European Association of Nuclear Medicine regard-

Keywords: allergy, diuretic renography, furosemide, safety

doi.org/10.2214/AJR.17.18801

Received July 25, 2017; accepted after revision September 1, 2017.

¹All authors: Department of Radiology, Massachusetts General Hospital, 55 Fruit St, Wht 4-427, Boston, MA 02114. Address correspondence to Y. Wang (ywang34@partners.org).

AJR 2018; 210:866–868

0361–803X/18/2104–866

© American Roentgen Ray Society

Safety of Diuretic Renography

ing the appropriateness of furosemide usage in the setting of reported sulfonamide allergies. The absence of prescriptive guidelines from the major nuclear medicine societies has contributed to practice variation among nuclear physicians, which can be frustrating for referring physicians and unnecessarily deny patients a potentially useful examination.

The purpose of this retrospective cohort study is to evaluate the safety of a single standardized IV injection of furosemide, administered as part of a diuretic renogram, in a large consecutive series of patients with reported sulfonamide allergies. Our goal is to standardize the practice patterns among our nuclear physicians.

Materials and Methods

This retrospective study was performed as part of a departmental quality improvement initiative. Approval from our institutional review board was obtained. Informed consent was waived.

Identification of Diuretic Renograms

We queried for renograms, with and without furosemide, performed at our institution in adult and pediatric patients between January 2009 and December 2015. This search was performed by using the radiology information system fields for the examination code maintained for billing purposes. For each such examination, data regarding the history of sulfonamide allergy, total number of reported allergies, and dose of furosemide prescribed during diuretic renography were extracted by using a programmatic interface to the electronic medical record.

Identification of Reactions Reported Following Diuretic Renography

The electronic health record (EHR) was queried for any medical visit within 30 days after the diuretic renogram was performed. Any clinical notes during this period were queried for any of the following search terms: "allergy," "allergic," "reaction," "rash," "redness," "hives," "pruritus," "shortness of breath," "chest pain," "fever," "wheezing," "gastrointestinal upset," "nausea," and "vomiting." The radiology report issued as part of the diuretic renogram examination was also queried for the aforementioned search terms to capture any immediate reactions. Clinical notes containing any of these search terms were manually reviewed to identify possible reactions. Separate internal nuclear pharmacy records were also reviewed for symptoms observed during a renogram study or reported directly to our department.

Diuretic Renography

All renograms were performed with a dose of 10 mCi (370 MBq) of ^{99m}Tc -labeled mertiatide. Diuretic renography was performed with the IV administration of 0.04 mg/kg of furosemide, given at 20 minutes after tracer injection. Our present departmental policy in patients with a reported sulfonamide allergy is to prescribe furosemide at the discretion of the supervising nuclear physician and referring physician. Furosemide is not administered if an anaphylactic reaction to any sulfonamide agent has been reported.

Results

A query of our radiology information systems database showed that 1403 patients underwent a renogram between January 2009 and December 2015. Nine percent (127/1403) of patients had a reported history of sulfonamide allergy at the time of examination. Reactions to any sulfonamide drug documented as occurring more than 1 month after nuclear renography were excluded.

Of the examinations, 1103 were performed as diuretic renograms and 299 were performed as nondiuretic renograms, with protocoling at the discretion of the radiologist or the referring physician. Eighty-three of 1103 diuretic renograms (7.5%) were performed for patients with a history of sulfonamide allergies. Among patients with a history of sulfonamide allergy, 59.0% (49/83) reported mild reactions (rash, hives, gastrointestinal upset, or syncope) related to trimethoprim sulfamethoxazole antibiotic, 3.6% (3/83) had mild reactions to an unknown sulfonamide drug, and 37.3% (31/83) of patients had unknown reaction type to unknown sulfonamide drug but did not recall experiencing any symptoms characteristic of anaphylaxis at direct interview. No specific allergies to furosemide were documented or verbally reported by any patient.

Nondiuretic renograms were performed 44/299 (14.7%) on patients with a history of sulfonamide allergies. Among these patients, 40.9% (18/44) had reported mild reactions (rash, hives, weird feeling, or gastrointestinal upset) to trimethoprim sulfamethoxazole antibiotic, 15.9% (7/44) of patients had mild reactions to unknown sulfonamide drug, and 43.1% (19/44) of patients had unknown reaction type to unknown sulfonamide drug.

Two hundred thirty-two renograms were performed on pediatric patients (< 18 years old). Among these, 217 were diuretic renograms

and 15 were nondiuretic renograms. Among pediatric diuretic renograms, 13 patients had documented history of allergy to trimethoprim sulfamethoxazole antibiotic. Among pediatric nondiuretic renograms, two patients had documented history of allergy to trimethoprim sulfamethoxazole antibiotic.

The mean ($\pm$ SD) dose of furosemide administered to adult patients was 23.2 ± 6.5 mg. The mean dose of furosemide administered to pediatric patients was 8.4 ± 5.7 mg.

The EHR query and internal nuclear pharmacy record review revealed two cases of suspected reactions related to diuretic renography. In the first case, a 50-year-old woman presented to the emergency department 1 day after undergoing a diuretic renogram for rash on her chest that developed after the examination and in the setting of a week-long cough, congestion, and sore throat. She was treated with oral diphenhydramine for her rash and supportive care for her presumed upper respiratory infection. The patient also reported her symptoms to our department, and a reaction report was filed by our nuclear pharmacist. She received 28.8 mg of furosemide as part of her renogram.

In the second case, the mother of a 19-month-old boy reported a rash on his upper and lower extremities immediately after he completed imaging for a diuretic renogram. He was referred to his pediatric urologist for further evaluation and management. The child had no history of allergy and no prior exposure to sulfonamide drugs. His symptoms were considered indicative of an allergic reaction, and allergy to furosemide was added to his EHR. He received 7.1 mg of furosemide as part of his renogram.

In a separate incident, an 18-year-old woman reported to our department that she fainted several hours after undergoing diuretic renography. She had a history of mild allergy to sulfonamide antibiotics, but had previously received furosemide without adverse effects. She was evaluated by her urologist at a same-day routine visit for her chronic ureteropelvic junction obstruction. Her symptoms were considered very unlikely to be related to an allergic reaction to furosemide. She received 21.6 mg of furosemide as part of her renogram.

No other suspected reactions were uncovered by the EHR query within a 30-day period after any diuretic or nondiuretic renogram.

Discussion

Allergies to sulfonamides are common. Approximately 10% of patients referred for nuclear renography at our institution have a reported history of allergy to sulfonamide drugs, although the nature of the reaction and specific drug exposure is inconsistently recalled by the patient or documented in the EHR. This rate is higher than that of the general population, which is reported as 2.2–3.4% [5].

Our series includes a total of 88 diuretic renograms performed on patients with a reported history of allergy to sulfonamide drugs. Three potential adverse drug effects were reported in the 30-day period after diuretic renogram. The report of fainting after a diuretic renography was considered by the emergency department physicians to be very unlikely to represent an allergic reaction; fainting may have resulted from dehydration secondary to diuretic administration. Two other incidents involved the development of a rash and likely were related furosemide reactions. Both were treated with a single dose of oral diphenhydramine, resulting in resolution of symptoms and physical manifestations. Overall, the reaction rate was very low at 2.3% (2/88). More important, no serious reactions occurred.

Although the sample of adverse reactions is too small to reliably determine whether the dose of furosemide statistically affected the likelihood of developing drug effects, the doses administered to the three patients re-

porting events were within 1 SD above and below mean doses given to that age group.

An important limitation of our study was the retrospective technique. Among the 299 nondiuretic renograms performed during the study period, 44 were performed on patients with a documented history of allergy to sulfonamide drugs at the discretion of the nuclear physician or referring physician. The rationale for why furosemide was not administered for the other 255 examinations is not available in the EHR or internal departmental records. As a result, we could not account for instances in which the referring physician was aware of a severe reaction of sulfonamide drug that was documented in the EHR or reported verbally by the patient. As expected, no incidents were reported after any nondiuretic renogram.

Although this study is limited to a single center, our hospital is a tertiary-care facility that serves a very large and diverse population. Our hospital is also part of an expansive statewide medical network with integrated EHR, so we expect to capture many potential drug effects after renograms, even if they were reported to local medical facilities. It is possible that we missed a small number of events that occurred in patients coming from other parts of the country or overseas, though likely with inconsequential effect on our results.

Conclusion

On the basis of our institutional experience, we conclude that the standard admin-

istration of furosemide during a nuclear renogram is associated with an extremely low risk of minor adverse events and negligible risk of serious adverse events, even in a cohort in whom a substantial subset of patients had prior reactions of unknown severity. We propose that it is appropriate to screen patients referred for nuclear renograms for history of allergies to sulfonamide drugs through a query of the EHR and direct patient interview, but to withhold furosemide, if otherwise indicated, only if a moderate-to-severe reaction to any sulfonamide drug is documented or recalled.

References

1. Strom BL, Schinnar R, Apter AJ, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med* 2003; 349:1628–1635
2. Slatore CG, Tilles SA. Sulfonamide hypersensitivity. *Immunol Allergy Clin North Am* 2004; 24:477–490 [vii]
3. Ahmad A, Ramakrishnan A, McLean MA, et al. Use of optical biosensor technology to study immunological cross-reactivity between different sulfonamide drugs. *Anal Biochem* 2002; 300:177–184
4. Hansbrough JR, Wedner HJ, Chaplin DD. Anaphylaxis to intravenous furosemide. *J Allergy Clin Immunol* 1987; 80:538–541
5. Macy E, Poon KYT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med* 2009; 122:778.e1–778.e7