Diuretic Renal Scintigraphy in Patients with Sulfonamide Allergies: Possible Alternative Use of Ethacrynic Acid.

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Word Count: 999

Financial Support: None
Disclosures: Nothing to disclose

Short running title: Ethacrynic Acid for Renal Scintigraphy
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Abstract

Furosemide may trigger life threatening sulfonamide cross-hypersensitivity reactions, posing an imaging decision dilemma for patients who need diuretic renal scintigraphy. **Methods:** The authors present the experience using ethacrynic acid as a non-sulfonamide alternative diuretic in five patients with discussion of diuretic molecular structure, potential side effects, protocol development and imaging results. **Results:** Diuretic renal scintigraphy using ethacrynic acid provided useful information about the obstructive syndrome status in all cases with no adverse clinical impact. **Conclusion:** Ethacrynic acid is a potential alternative to furosemide for patients with severe sulfonamide reactions.

Key words: Ethacrynic Acid, Diuretic Renal Scintigraphy, Sulfonamide allergy.
The objective of this essay is to raise awareness of ethacrynic acid as a possible alternative to furosemide for provocative diuretic renal scintigraphy. We retrospectively report on the experience with five patients, describing protocol development, patient safety, and diagnostic value with regards to conventional diuretic renal scintigraphy.

Materials and Methods

Our institutional review board approved this retrospective study and the requirement to obtain informed consent was waived. Between October 2009 and May 2014, three male and two female patients underwent diuretic renal scintigraphy using ethacrynic acid as an alternative to furosemide. Each patient had known prior severe sulfonamide reaction included hives, tongue swelling, respiratory distress, vomiting, oral pruritus and giant hives. The patient’s ages were 25, 54, 66, 83 and 84 years. Three patients presented with hydronephrosis and recurrent urinary tract infections, the fourth one with remote pyeloplasty and intermittent flank pain, and the fifth one with nephrolithiasis and hydronephrosis. Each patient received a standard adult dose of 370 MBq (10 mCi) of technetium 99m-MAG3 (mercaptoacetyltriglycine) intravenously with routine dynamic and sequential planar gamma camera imaging. Thirty minutes after radiotracer injection, 25 mg of ethacrynic acid in 50 mL of 5% dextrose water were infused
intravenously over 15 minutes. The post diuretic imaging is initiated after completion of ethacrynic acid infusion and continued for 30 minutes.

**Results**

Of the five exams, one was positive for a left renal collecting system obstruction (figure 1). All the remainder 4 cases had no obstructive uropathy. Four patients had a technically excellent diuretic renal imaging. One exam was technically challenging to quantify the half-time of radiotracer clearance values secondary to little activity in the collecting system yet visually negative for collecting system obstruction. There were no reported adverse reactions to ethacrynic acid.

**Discussion**

In patients with known severe allergy to sulfonamides, radiologists and nuclear medicine physicians face the difficult choice of using or bypassing the use of Furosemide for diuretic renal scintigraphy. Furosemide may induce sulfonamide hypersensitivity reactions ranging from fever to life threatening events such as hepatic necrosis and Stevens-Johnson syndrome. Sulfonamide (sulfa) reactions occur in 3-6% of the general population and up to 60% of those with human immunodeficiency virus (1). Although the mechanism may not be a true cross-reaction, patients with hypersensitivity reactions to antibiotic sulfonamides, react to nonantibiotic sulfonamides such as furosemide with a frequency approaching 10% (2-4). When the sulfa allergic patient presents for diuretic renal scintigraphy, present imaging management has two options: (a) administering furosemide
regardless of known sulfamide reaction and relying on facts that cross-reactions are rare and often mild, or (b) performing a non-diuretic renal scintigraphy not fulfilling the evaluation of obstructive uropathy. A review for alternatives to furosemide reveals a sulfa moiety in many diuretics including thiazides, carbonic anhydrase inhibitors and most proximal loop diuretics including azosemide, bumetanide and torasemide (5). The exception is ethacrynic acid, a rapid acting loop diuretic available for intravenous administration (figure 2). This makes ethacrynic acid an ideal diuretic alternative for renal scintigraphy of patients with severe sulfonamide allergies (6-7). The major risk factor to consider when using intravenous ethacrynic acid is immediate volume depletion, a relevant life threatening reaction for one-time use, requiring blood pressure monitoring. Attention to ototoxicity is important which can cause temporary hearing loss and even deafness, particularly when paired with aminoglycoside antibiotics. Less concerning reactions, with repeated use, include hypokalemic metabolic alkalosis and magnesium depletion (8-10).

To confirm or rule out obstructive uropathy in patients with known severe sulfonamide allergies, a diagnostic imaging protocol for ethacrynic acid was developed with input from our pharmacy department. Ethacrynic acid has nearly 100% bioavailability with a steeper dose-response curve than furosemide. With intravenous injection, onset of action is 5 minutes with peak diuretic effect occurring within 30 minutes (11). Clinically, intravenous ethacrynic acid weight
based dose is 0.5-1 mg/kg, not to exceed 100 mg in a single dose (12). A typical patient with pulmonary edema may receive 25-50 mg of ethacrynic acid intravenously over 20-30 minutes. To minimize the dose risk yet provide a brisk diuretic effect, we chose 25 mg of ethacrynic acid in 50 mL of 5% dextrose water infused intravenously over a slightly shorter period of 15 minutes. The post diuretic image acquisitions were set to initiate after completion of ethacrynic acid infusion and continued for 30 minutes.

Post diuretic imaging of the 5 cases provided adequate answer to the presence or absence of obstructive uropathy (figure 1 & 3). Our limited series further support the initial short report on ethacrynic acid use for diuretic renal scintigraphy (13). The advantages of using ethacrynic acid in diuretic renal scintigraphy are its availability, relative simplicity of administration, absence of negative clinical impact for its one-time use, and most of all, ability to fully assess the presence or absence of obstructive uropathy in patients with sulfa allergy. The main drawback resides in its cost of $300-$600 for a 25-mg intravenous dose. Overall, when the diagnosis of obstructive uropathy is crucial for the patient care, the cost of ethacrynic acid probably is counterbalanced by all its imaging benefits avoiding the recourse to any other less performant imaging modalities or invasive urologic procedures. This study is successful as a proof of concept and more research is necessary to establish ethacrynic acid as a
substitute to furosemide for diuretic scintigraphy in instances of severe sulfa allergy.

References


Figure 1

A 83-year-old male with a severe sulfa allergy, benign prostatic hyperplasia, left hydronephrosis and recurrent urinary tract infections. Pre-diuretic imaging (not shown) demonstrated prominent tracer activity in the left pyelocaliciel structures suspicious for obstruction. Post-diuretic imaging with ethacrynic acid in upright position showed a prolonged left T half of 29 minutes with persistent left hydronephrosis consistent with an urodynamically significant left obstruction. Normal right renal post-ethacrynic acid diuretic challenge.
Sulfonamide drugs share a common sulfur moiety (SO2NHR) attached to a benzene ring. Sulfonamide antibiotics (upper boxes) have an arylamine at the N4 position which incites metabolites responsible for allergic reactions. The diuretics bumetanide, furosemide and torsemide all have molecularly similar N4 sites that can cross-react and harm the allergic patient. Ethacrynic acid (lower box) does not contain a sulfonamide group.
Figure 3

A 25-year-old male with a severe sulfa allergy and history of urinary bladder extrophy, status post closure, ureteral reimplant and subsequent appendicovesicostomy, presenting with left hydronephrosis and recurrent urinary tract infections. Pre-diuretic renal scintigraphy (not shown) demonstrated prominent activity in the left collecting system suspicious for obstruction. Diuretic challenge using ethacrynic acid showed satisfactory emptying of both collecting systems with a half-time value of 3.8 and 4.7 minutes on the right and left sides respectively ruling out obstructive uropathy.
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Published online: October 15, 2015.
Doi: 10.2967/jnmt.115.161331

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http://tech.snmjournals.org/content/early/2015/10/14/jnmt.115.161331

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