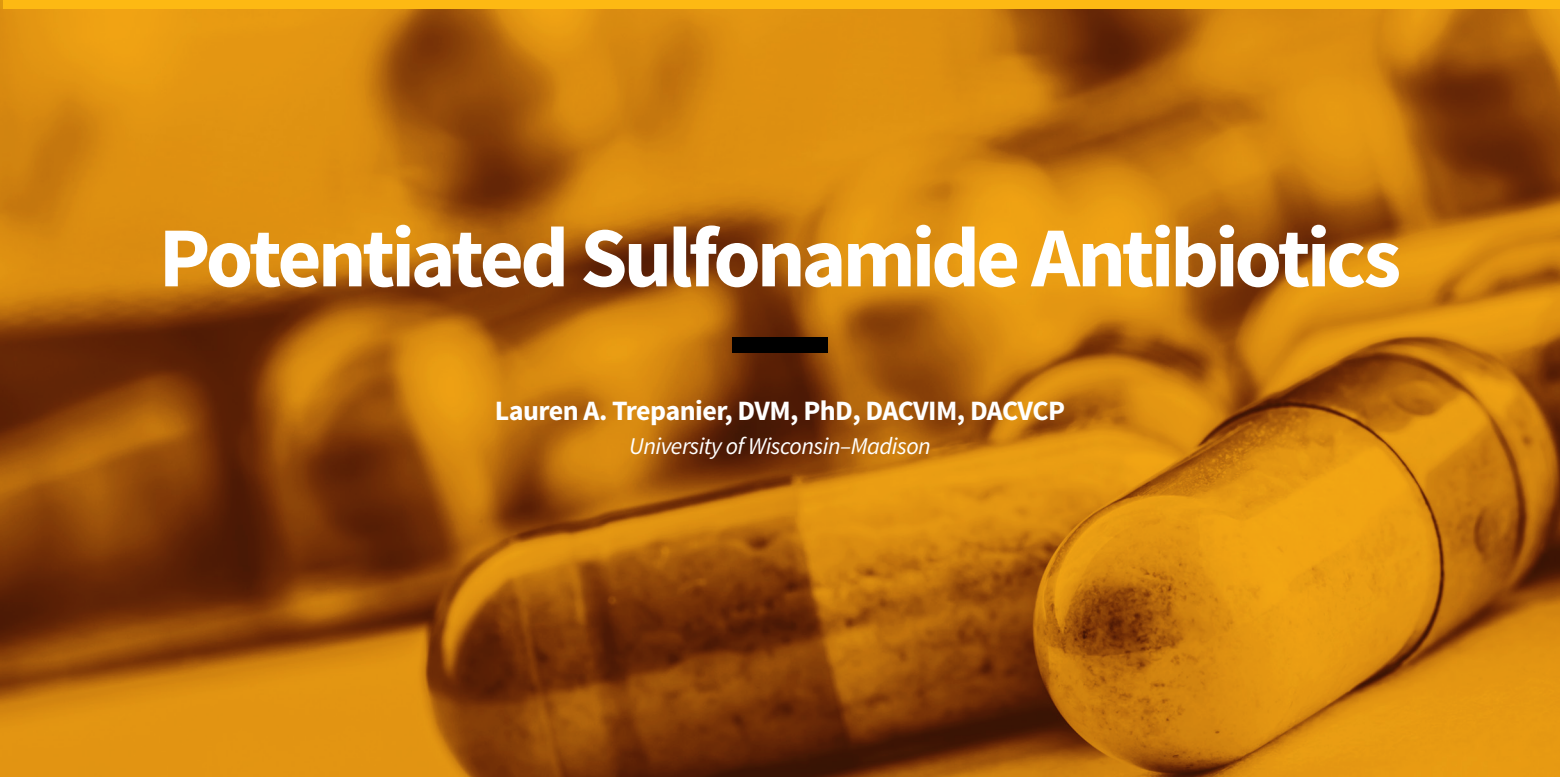

Potentiated Sulfonamide Antibiotics

Lauren A. Trepanier, DVM, PhD, DACVIM, DACVCP
University of Wisconsin–Madison

Overview

- Potentiated sulfonamides are broad-spectrum antibacterial and antiprotozoal agents that inhibit bacterial folate synthesis and have been used for more than 50 years.
- Because of associated adverse events, these drugs are predominantly used in veterinary medicine to treat resistant infections of the skin, urinary tract, or respiratory tree.

Toxicities

Dose Dependent

- Keratoconjunctivitis sicca (KCS)
  - Occurs in ≈15% of dogs[1]
  - May be reversible with early drug discontinuation[2]
- Folate deficiency
  - Nonregenerative anemia, often normocytic and normochromic, with prolonged administration[3]
- Drug-induced hypothyroidism
  - Antimicrobial sulfonamides reversibly inhibit thyroid peroxidase.[4]
  - May interfere with thyroid hormone synthesis with prolonged high-dose administration (6 weeks) in dogs[5]
  - Clinical hypothyroidism can develop with chronic use.[6]

Idiosyncratic

- Acute idiosyncratic toxicities (eg, drug hypersensitivity reactions) typically develop between 5 days and 4 weeks of treatment (median onset, 12 days).[7]
  - Clinical signs may be noted immediately after a 7- to 10-day course of sulfonamide antibiotic treatment.[7]
  - Signs can be seen earlier than 5 days in dogs previously exposed to potentiated sulfonamides.
- Idiosyncratic sulfonamide reactions in dogs appear to be immune-mediated and caused by a reactive metabolite of the sulfonamide antibiotic that binds to tissue proteins and acts as a hapten.[8]
- Incidence is unclear.
- Clinical signs can include
  - Fever[7]
  - Blood dyscrasias[7-9]
    - Regenerative immune-mediated thrombocytopenia
    - Immune-mediated hemolytic anemia
    - Transient neutropenia

KCS = keratoconjunctivitis sicca

- Skin eruptions[10]
  - Range in severity from erythema and pruritus to toxic epidermal necrolysis
- Acute hepatopathy
  - Often moderate-to-severe increases in ALT levels can occur in patients with acute parenchymal damage[7]
  - May also present with or progress to cholestatic changes (author's observations)
- Polyarthropathy[11-17]
  - Clinically resembles Lyme disease or primary immune-mediated polyarthropathy
    - Involves distal joints (eg, elbow, stifle, carpal, tarsal)
    - Nonseptic polyarthritis, with synovial fluid containing a predominance of nontoxic neutrophils without the presence of organisms
  - Improvement is seen 1 to 3 days after discontinuation of sulfonamide antibiotics, with or without glucocorticoid administration.
  - Doberman pinschers are overrepresented.[11,12,18,19]
    - Additional signs of lymphadenopathy, retinitis, protein-losing nephropathy, leukopenia, and modest thrombocytopenia may be seen.[11]
- Proteinuria
  - May be severe but is rapidly reversible with drug discontinuation[20]

Monitoring

- Weekly baseline Schirmer tear test if treatment will extend beyond 10 days
  - Instruct owners to monitor daily for mucoid ocular discharge, redness, or blepharospasm.
- Monitor for clinical signs of hypothyroidism if prolonged treatment (6 weeks or longer) is needed.
- For administration longer than 3 weeks, consider monitoring CBC every 1 to 2 weeks and checking serum folate if new anemia is noted.
- Instruct owners to monitor for signs of drug hypersensitivity, including
  - Pallor, petechiae, or fever
  - New or worsening skin lesions
  - Jaundice, GI upset, or dark urine
  - Shifting leg lameness

ALT = alanine aminotransferase
KCS = keratoconjunctivitis sicca
SAMe = *S*-adenosylmethionine

All potentiated sulfonamide antibiotics commercially available in the United States have been implicated in cases of sulfonamide hypersensitivity.

- Client education is the most important monitoring tool, as idiosyncratic toxicities can develop acutely between routine rechecks.

Management of Adverse Events

- At first signs of KCS, discontinue drug and treat patient with topical immunomodulator (eg, cyclosporine, tacrolimus) and artificial tears.
  - Sulfonamide-induced KCS is often reversible with early drug discontinuation.
- Nonregenerative anemia associated with chronic use can be prevented by coadministration of folinic (but not folic) acid.
- Because idiosyncratic toxicities do not respond to dose reduction, discontinue sulfonamide antibiotic at first sign of a potential adverse event.
  - Evaluate patient as soon as possible.
  - Include careful examination for ocular lesions, petechiae, jaundice, skin eruptions, joint effusion, hematuria, melena, and oral or mucocutaneous ulcerations.
  - Screen with CBC, serum chemistry profile, and urinalysis.
  - Consider treating with glutathione precursor (eg, oral *S*-adenosylmethionine [SAMe], IV *N*-acetylcysteine) to help decrease haptenization of the reactive sulfonamide metabolite.
  - If response to drug discontinuation and glutathione precursors is poor after 24 to 48 hours, consider short course of immunosuppressive glucocorticoids.
- Although dogs with thrombocytopenia or hepatopathies have a more guarded outcome, even those with severe clinical manifestations can survive with good clinical support.[7]

Reexposure Risk

- All potentiated sulfonamide antibiotics commercially available in the United States have been implicated in cases of sulfonamide hypersensitivity.
  - Trimethoprim–sulfadiazine
  - Ormetoprim–sulfadimethoxine
  - Trimethoprim–sulfamethoxazole (human generic formulations)
- There is no evidence of cross-reactivity with other sulfonamide-containing drugs that have different underlying structures (eg, acetazolamide, furosemide, glipizide, hydrochlorothiazide).[21,22]
  - Drug hypersensitivity to sulfonamide antibiotics is mediated by a different part of the molecule (ie, an arylamine ring) and not by the sulfonamide moiety.
  - No evidence supports avoidance of nonantibiotic sulfonamides in dogs with a history of idiosyncratic toxicity to potentiated sulfonamide antibiotics.[21,22]

LAUREN A. TREPANIER, DVM, PhD, DACVIM, DACVCP, is an internist and clinical pharmacologist at University of Wisconsin–Madison. Her clinical interests include pharmacology and therapeutics, with special emphasis on adverse drug reactions and interactions.

References

1. Berger SL, Scagliotti RH, Lund EM. A quantitative study of the effects of Tribrissen on canine tear production. *JAAHA*. 1995;31(3):236-241.
2. Morgan RV, Bachrach A Jr. Keratoconjunctivitis sicca associated with sulfonamide therapy in dogs. *JAVMA*. 1982;180(4):432-434.
3. Lording PM, Bellany JEC. Trimethoprim and sulfadiazine: adverse effects of long term administration in dogs. *JAAHA*. 1978;14(3):410-417.
4. Doerge DR, Decker CJ. Inhibition of peroxidase-catalyzed reactions by arylamines: mechanism for the anti-thyroid action of sulfamethazine. *Chem Res Toxicol*. 1994;7(2):164-169.
5. Hall IA, Campbell KL, Chambers MD, Davis CN. Effect of trimethoprim/sulfamethoxazole on thyroid function in dogs with pyoderma. *JAVMA*. 1993;202(12):1959-1962.
6. Gookin JL, Trepanier LA, Bunch SE. Clinical hypothyroidism associated with trimethoprim-sulfadiazine administration in a dog. *JAVMA*. 1999;214(7):1028-1031.
7. Trepanier LA, Danhof R, Toll J, Watrous D. Clinical findings in 40 dogs with hypersensitivity associated with administration of potentiated sulfonamides. *JVIM*. 2003;17(5):647-652.
8. Trepanier LA. Delayed hypersensitivity reactions to sulphonamides: syndromes, pathogenesis, and management. *Vet Dermatol*. 1999;10(3):241-248.
9. Fox LE, Ford S, Alleman AR, Homer BL, Harvey JW. Aplastic anemia associated with prolonged high-dose trimethoprim-sulfadiazine administration in two dogs. *Vet Clin Pathol*. 1993;22(3):89-92.
10. Kunkle GA, Sundlof S, Keisling K. Adverse side effects of oral antibacterial therapy in dogs and cats: an epidemiologic study of pet owners' observations. *JAAHA*. 1995;31(1):46-55.
11. Giger U, Werner LL, Millichamp NJ, Gorman NT. Sulfadiazine-induced allergy in six Doberman pinschers. *JAVMA*. 1985;186(5):479-484.
12. Gray A. Trimethoprim-sulphonamide hypersensitivity in dogs. *Vet Rec*. 1990;127(23):579-580.
13. Grondalen J. Trimethoprim-sulphonamide induced polyarthritis. *Vet Rec*. 1987;121(7):155.
14. Harvey RG. Possible sulphadiazine-trimethoprim induced polyarthritis. *Vet Rec*. 1987;120(22):537-538.
15. Lees GE, Rogers KS, Troy GC. Polyarthritis associated with sulfadiazine administration in a Labrador retriever dog. *Southwestern Vet*. 1986;37(1):13-17.
16. Medleau L, Shanley KJ, Rakich PM, Goldschmidt MH. Trimethoprim-sulfonamide-associated drug eruptions in dogs. *JAAHA*. 1990;26(3):305-311.
17. Werner LL, Bright JM. Drug-induced immune hypersensitivity disorders in two dogs treated with trimethoprim sulfadiazine: case reports and drug challenge studies. *JAAHA*. 1983;19(5):783-790.
18. Whur P. Possible trimethoprim-sulphonamide induced polyarthritis. *Vet Rec*. 1987;121(4):91-92.
19. Cribb AE, Spielberg SP. An in vitro investigation of predisposition to sulphonamide idiosyncratic toxicity in dogs. *Vet Res Commun*. 1990;14(3):241-252.
20. Vasilopulos RJ, Mackin A, Lavergne SN, Trepanier LA. Nephrotic syndrome associated with administration of sulfadimethoxine/ormetoprim in a Dobermann. *J Small Anim Pract*. 2005;46(5):232-236.
21. Strom BL, Schinnar R, Apter AJ, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med*. 2003;349(17):1628-1635.
22. Uetrecht J. N-oxidation of drugs associated with idiosyncratic drug reactions. *Drug Metab Rev*. 2002;34(3):651-665.

Client education is the most important monitoring tool, as idiosyncratic toxicities to sulfonamide antibiotics can develop acutely between routine rechecks.