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 dogs¹
  - May be reversible with early drug discontinuation²
- Folate deficiency
  - Nonregenerative anemia, often normocytic and normochromic, with prolonged administration³
- Drug-induced hypothyroidism
  - Antimicrobial sulfonamides reversibly inhibit thyroid peroxidase.⁴
  - May interfere with thyroid hormone synthesis with prolonged high-dose administration (6 weeks) in dogs⁵
  - 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
  - Fever⁷
  - Blood dyscrasias⁷-⁹
    - Regenerative immune-mediated thrombocytopenia
    - Immune-mediated hemolytic anemia
    - Transient neutropenia

KCS = keratoconjunctivitis sicca
• Skin eruptions
  – 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\(^1,11-17\)
  – 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

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 \(\text{S}-\text{adenosylmethionine} \text{ (SAMe)}, \text{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).
- 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.  

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References

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