WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 9, 1295-1305. Review Article ISSN 2277– 7105

A RECENT ADVANCES IN THE ANTIBACTERIAL POTENTIAL OF SULFADIAZINE: A REVIEW

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Article Received on
12 April 2023,

Revised on 02 May 2023,
Accepted on 22 May 2023

DOI: 10.20959/wjpr20239-28350

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ABSTRACT

As a sulphonamide, sulfadiazine is formed when a 4-aminobenzenesulfonamido group is attached to the 2-position of pyrimidine. This review was based on the recent advances in the antibacterial potential of sulfadiazine for that an extensive literature survey was done. It acts as an antibiotic, an anti-infective, an antiprotozoal medication, a coccidiostat, a xenobiotic, a pollutant in the environment, and a drug allergen. It is a sulphonamide antibiotic, a modified aniline, and a pyrimidine. It shares some properties with a sulphanilamide. Sulfadiazine is an effective sulphonamide antibacterial medication for treating low- and moderate-severity infections caused by sensitive microorganisms. Sulfadiazine is effective against Chlamydia trachomatis but has little effect on other staph infections. Many protozoa are susceptible to sulphonamides, and they are effective against them. The bacterial enzyme dihydropteroate synthetase is essential for the synthesis of dihydrofolic acid, and it is inhibited by the sulphonamides, which are structural analogues of para-aminobenzoic acid (PABA). Sulfadiazine belongs to sulphonamide category of antimicrobials. Antibacterial activity of sulfadiazine has been well confirmed from the above literature survey which used in different dosage forms i.e., ointment, nano emulsion etc. It has exhibited for increased level of efficacy at different microbial strains. Due to its severe toxicity, sulfadiazine is prescribed with precaution in the cure of microbial infections. In concludes, sulfadiazine is old but effective antimicrobial agent that can be used in transdermal patch or film dosage form too.

KEYWORDS: Sulfadiazine, Antibacterial, Toxicity, Antibiotic-resistant, Metals.

INTRODUCTION

Sulfadiazine

As a sulphonamide, sulfadiazine is formed when a 4-aminobenzenesulfonamido group is attached to the 2-position of pyrimidine.[1] It acts as an antibiotic, an anti-infective, an antiprotozoal medication, a coccidiostat, a xenobiotic, a pollutant in the environment, and a drug allergen.[2] It is a sulphonamide antibiotic, a modified aniline, and a pyrimidine. It shares some properties with a sulfanilamide. The acid is a sulfadiazinate conjugate.[3]

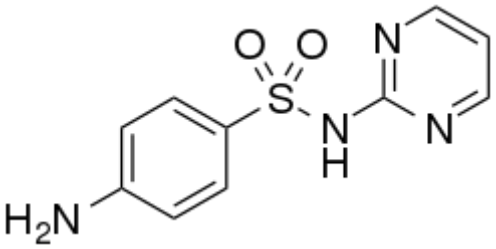

Fig. 1: Structure of sulfadiazine.

***IUPAC name*:** 4-amino-*N*-pyrimidin-2-ylbenzenesulfonamide

Molecular formula: $C_{10}H_{10}N_4O_2S$

Molecular weight: 250.28 g/mol

Melting point: 255.5 °C

A prescription antibacterial medication, sulfadiazine has been approved by the FDA for the treatment of bacterial infections such as chancroid, Toxoplasma gondii encephalitis, urinary tract infections, and others. Sulfadiazine is an effective sulfonamide antibacterial medication for treating low- and moderate-severity infections caused by sensitive microorganisms. It is generally recognized that sulfadiazine, like other sulfonamides, can produce clinically evident, non-generic liver damage.[4]

In vitro, the sulfonamides exhibit widespread antibacterial action. However, due to resistance, their usage in clinical settings has been limited. The majority of staphylococci and streptococci, as well as other gram-positive cocci, are susceptible to their effects. Unfortunately, sulfonamides are ineffective against enterococci.[5] Also vulnerable are gram-positive bacilli. Sulfonamides are effective against many gram-negative bacteria, including those in the family Enterobacteriaceae. This family includes such well-known pathogens as Escherichia coli, Enterobacter, Klebsiella, Proteus, and Salmonella. This class of medicines is also effective against most pseudomonas bacteria.[6] Sulfadiazine is effective against

Chlamydia trachomatis but has little effect on other staph infections. Many protozoa are susceptible to sulfonamides, and they are effective against them.[7]

Mode of action

Dihydrofolic acid can be synthesized by bacteria, but mammalian cells require an active transport system to accumulate it. The bacterial enzyme dihydropteroate synthetase is essential for the synthesis of dihydrofolic acid, and it is inhibited by the sulfonamides, which are structural analogues of para-aminobenzoic acid (PABA). Sulfadiazine's method of action includes the formation of pteroate analogs that can be integrated into the folic acid molecule, but this is a secondary effect.[8]

Antimicrobial properties

- **Fatima et al. (2022)** created a nanoemulsion-based silver sulfadiazine cosmetotherapeutic lotion with enhanced antibacterial activity for the treatment of burn injuries, and study its efficacy. However, silver sulfadiazine's poor solubility, low absorption, and other hematologic consequences severely limit its pharmaceutical applications and make it mostly used as a topical treatment for burn patients. The ultrasonication method was used to create the nanoformulation, and it was then optimized by changing the parameters and concentrations used to make the w/o emulsion. Particle size is reduced to 213 nm in the optimized formulation, with an encapsulation effectiveness of almost 80%. Argan oil, used as a cosmetotherapeutic ingredient, was also incorporated into a nanoemulsion-based SSD lotion, which was then created for scar massage with enhanced penetration properties. Physical appearance, refractive index, particle size, encapsulation efficiency, and biocompatibility were all used to characterize the intended cosmeceutical formulation. FTIR (Fourier Transform Infrared Spectroscopy) was used to analyse the constituents of the formulation for compatibility. The SSD-containing nano lotion formulation outperformed commercial burn creams in antibacterial activity tests using a variety of bacterial strains.[9]

- **Catlyn et al. (2016)** We used an adenylate kinase reporter assay for bacterial cell death to screen a food and drug administration-approved drug library for members that exhibit bactericidal activity toward 72-h-established P. aeruginosa biofilms as a first step in identifying agents that may have a greater propensity to improve clearance of wound-associated bacterial pathogens. 34 different substances shown antibiofilm action. A. baumannii and S. aureus biofilm-associated bacteria counts were also demonstrated to be

decreased by zinc pyrithione, which also showed an additive benefit when combined with silver sulfadiazine, a popular topical treatment for wound site infections. In a mouse model of wound infection, the enhanced antibacterial activity of zinc pyrithione and silver sulfadiazine was sustained in an ointment formulation and resulted in increased clearance of P. aeruginosa, A. baumannii, and S. aureus. All things considered, these findings imply that topical zinc pyrithione and silver sulfadiazine combination formulations may slow the development of illness and wound-related bacterial infections.[10]

- **Hakan et al. (2013)** study used a rat model of a full-thickness burn lesion contaminated with multidrug-resistant Pseudomonas aeruginosa to evaluate the efficacy of four different topical antimicrobial dressings. Forty male Wistar albino adult rats were utilized. Antibacterial effects of daily application to a burn wound seeded 10 minutes earlier with 108 CFU (colony forming unit)/0.5 mL of a multi-drug resistant Pseudomonas aeruginosa strain: control group (group 1), silver sulfadiazine (1%), chlorhexidine acetate (0.5%), citric acid (3%) and silver-coated dressing (group 5). One "control" group and four "treatment" groups were evaluated. Histopathological evidence verified that all rats were subjected to third-degree burns. Significant variations were seen between Group 2 and Group 5 tissue cultures and the other 3 groups, however there were no differences between Groups 1, 3, and 4. The therapies were as effective as follows: The effectiveness of various treatments for preventing infection is compared as follows: 1% silver sulfadiazine > silver-coated dressing > 3% citric acid > 0.5% chlorhexidine acetate > control group. Infections brought on by multidrug-resistant Pseudomonas spp. were successfully treated with silver sulfadiazine and silver-coated dressing, as shown by our findings.[11]

- **Jason et al. (2007)** The combination of silver nitrate and sulfadiazine results in silver sulfadiazine, a topical antibacterial. The fluffy white powder is almost completely insoluble in water. The silver sulfadiazine in the commercial cream is in micronized form. It's a go-to for both partial- and full-thickness burns as an adjuvant in the fight against infection. By disrupting the integrity of the cell membrane or the cell wall, silver sulfadiazine is effective against a wide variety of bacteria (both gram-positive and gram-negative) and yeast.[12]

- **Schiavo et al. (2020)** Topical creams based on 0.1% polyhexanide and 1% silver sulfadiazine were compared for their in vitro antibacterial activity against Staphylococcus

aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, and a combination of S. aureus and K. pneumoniae.As a positive control, we employed a topical cream containing 0.1% gentamicin, while a blank white topical cream served as the negative control. Agar well-diffusion assay was used to assess antibacterial activity in vitro. The antimicrobial activity of 0.1% polyhexanide topical cream was compared to that of 1% silver sulfadiazine, as well as the negative and positive controls, using two-way Analysis of Variance (ANOVA) and the resulting P-values. All of the active topical creams that were evaluated for their derivatives were effective at reducing microbial strains. There was no statistically significant difference between the two topical creams' antibacterial activity against P. aeruginosa and E. coli, but the 0.1% polyhexanide cream was significantly more effective against S. aureus and K. pneumonia and the combination of S. aureus and K. pneumoniae. These findings lend credence to the use of a 0.1% Polyhexanide topical preparation for the treatment of infected or at-risk wounds, as it is non-inferior to silver sulfadiazine against some bacterial strains (P. aeruginosa and E. coli) and superior to others (S. aureus and K. pneumoniae).[13]

- **Klein et al. (1986)** Many researchers have expressed worry over the present minimum inhibitory concentration (MIC) test techniques for silver sufadiazine (AgSu) creams due to the reported growth of in vivo silver sulfadiazine-resistant organisms and inconsistencies noticed while testing antimicrobial creams. The use of sonication was investigated to see whether it might be used to render the test more accurate and reliable. The MBC of AgSu in Silvadene, a topical cream, is discussed along with a method for calculating it. Pseudomonas aeruginosa, Staphylococcus epidermidis, and Staphylococcus aureus isolates from the American Type Culture Collection (ATCC) were used to fine-tune the sonication process. The in vitro sensitivities of P aeruginosa and S aureus clinical isolates were then determined, including those of S aureus that had been found to be resistant in vivo to Silvadene. The sonication outcomes show that an aqueous, homogenous suspension of AgSu cream is created, allowing for precise and repeatable MBC activity assessment.[14]

- **Martin et al. (2017)** There is a critical need for brand new medications as a direct result of microbial resistance. The sulfa medication sulfadiazine and different salicylaldehydes served as starting materials for the synthesis of a series of Schiff bases. A 4-[(2-hydroxybenzylidene)amino] compound was produced.The cytotoxicity of -N-(pyrimidin-

2-yl)benzene-sulfonamides was tested against a variety of bacteria, fungi, and mycobacteria, including M. TB, M. kansasii, and M. avium. Minimum inhibitory concentration values started at 7.81 M for bacteria, with the species Staphylococcus, including methicillin-resistant S. aureus, showing the highest susceptibility. At concentrations as low as 1.95 M, the growth ofCandida sp. and Trichophyton interdigitale was suppressed.4-[(2,5-Dihydroxybenzylidene)amino]With no detectable cytotoxicity and a selectivity index more than 16, -N-(pyrimidin-2-yl)-benzenesulfonamide was shown to be the most selective Schiff base for these strains. The antibacterial and antifungal activities were enhanced by dihalogenation of the salicylic moiety, but the cytotoxicity was raised, especially with increasing atomic mass. Promising hits for further development of antimicrobial drugs are derivatives with improved characteristics over the basic sulfadiazine.[15]

- **Ullah et al. (2019)** Incorporating silver sulfadiazine into PAN nanofibers has been shown to improve their mechanical, structural, and antibacterial properties. Electrospun nanofibers with AgSD loaded for the first time were compared to PAN nanofibers with self-synthesized AgSD loaded by the solution immersion approach. FTIR was used to study the chemical interactions between the AgSD and PAN functional groups. SEM analysis of produced nanofiber mats revealed homogenous nanofibers devoid of bead formation, with well-defined morphology and surface characteristics. The addition of AgSD either in situ or through immersion slightly increased the nanofibers' diameter. Transmission electron microscopy was used to examine the nanoparticles' spatial distribution. The thermogravimetric analyzer confirmed that AgSD reduced the thermal stability of PAN, which is preferable from a medical standpoint. Nanofiber mats were found to have a crystalline structure using X-ray diffraction. X-ray photo spectroscopy was used to examine the presence of Ag and S in nanofiber mats. The disc diffusion method was used to study the antibacterial characteristics of nanofiber mats. Gram-negative bacteria were represented by the E. coli strain, and gram-positive bacteria by the Bacillus strain. The efficacy of AgSD emitted from PAN nanofiber mats was measured using zone inhibition assays against the bacteria. Both types of bacteria were used to test the antibacterial efficacy of PAN nanofibers impregnated with AgSD and compared to a control sample. Characterization results suggest that PAN/AgSD (immersion) nanofiber mats are superior to PAN/AgSD (in situ) mats in terms of structural and antibacterial

properties. Therefore, in our opinion, it is best to continue making nanofiber mats for antibacterial applications using self-synthesized AgSD.[16]

- **Elangovan et al. (2017)** Analytical data, IR, 1HNMR, 13CNMR, Fluorescence, UV-Vis spectra, and screening for anti-bacterial activities against Staphylococcus aureus and gram-negative bacteria Escherichia coli, Klebsiella aerogenes, and Bacillus subtilis, as well as anti-fungal activities against Aspergillus niger and Candida albicans by disc diffusion method, were collected. Standard antimicrobials for bacteria and yeasts included ciprofloxacin and nystatin.[17]

Resistance to sulfadiazine

Between 1965 and 1974, the ditch plate approach was used to evaluate sulphonamide resistance in clinical isolates during a clinical study of antimicrobial medicines in the treatment of burns victims in Birmingham. SSD was first used there in 1969, but only on patients with minor burns until 1972. After that year, it was also used on patients with more severe burns.[18]

Sulphonamide-resistant strains of Acinetobacter anitratus, Klebsiella spp., Escherichia coli, Enterobacter spp., Proteus mirabilis, and other Proteus species were more frequently recovered in 1974.[19] The agar dilution method showed that the MICs for some of these species were higher than 1000 mg sulphadiazine/liter. Strains recovered from SSD-treated patients were more likely to be resistant to sulphadiazine (41/59, 70%) than those recovered from SN-treated patients (23/50, 44%). SSD cream was put on hold, and the use of systemic sulphonamides and co-trimoxazole was restricted because of the rise in sulphonamide-resistant gram-negative bacteria. This situation would not improve until the proportion of sulphonamide-resistant isolates decreased.[20]

How metals effectively combat antimicrobial resistance

Angelo et al. (2023) There is a long tradition of using free metal ions as germicides. However, environmental bacteria exposed to high metal concentrations in highly polluted industrial soils or agricultural soil irrigated with polluted water have been observed to exhibit metal-resistance genes. Metals include Copper, Silver, Zinc etc.[21]

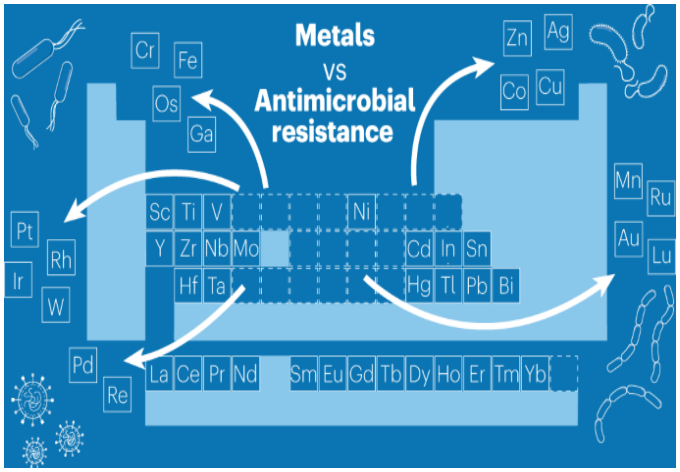

Fig. 3: Effects on metals in antimicrobial resistance.

It's promising that dozens of metal complexes are currently undergoing clinical trials for additional reasons, but the efficacy of metalloantibiotics in saving and protecting humans and animals from severe bacterial infections is still up for debate.

Toxicity of sulfadiazine

Like other sulfonamides, sulfadiazine causes a liver injury with some of the hallmarks of an allergy or hypersensitivity to the drug. Within a few days or weeks of starting the medicine, the typical onset is a quick onset of fever, rash, and jaundice. Although hepatocellular injury is most common in fatal instances, cholestatic injury can last for a long time. This clinical picture fits the criteria for DRESS syndrome (drug rash with eosinophilia and systemic symptoms), in which eosinophilia or atypical lymphocytosis are also present. Sulfadiazine has also been linked to reports of Stevens-Johnson syndrome. Many cases of acute liver failure have been connected to sulfonamides like sulfadiazine, and the sulfonamides continue to be among the top 5–10 causes of drug-induced, idiosyncratic fulminant hepatic failure. However, unless cholestasis is severe, most cases of sulfonamide-induced liver impairment heal fast, usually within 2 to 4 weeks. Rechallenge accelerates the onset of damage, and symptoms may emerge as soon as a day after reexposure. Patients who develop sulfadiazine-related liver damage may have had earlier, non-injurious exposure to the drug. Mild and temporary ALT rises that do not develop to jaundice or more severe liver impairment can also be caused by sulfonamides like sulfadiazine, either on their own or as part of a widespread hypersensitivity reaction. There is additional evidence that sulfonamides can cause granulomas in the liver.[22]

CONCLUSION

Sulfadiazine belongs to sulphonamide category of antimicrobials. Antibacterial activity of sulfadiazine has been well confirmed from the above literature survey which used in different dosage forms i.e., ointment, nano emulsion etc. It has exhibited for increased level of efficacy at different microbial strains. Due to its severe toxicity, sulfadiazine is prescribed with precaution in the cure of microbial infections. In concludes, sulfadiazine is old but effective antimicrobial agent that can be used in transdermal patch or film dosage form too.

Funding

Nil.

Conflict of interest

None.

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