Cutting's Handbook of Pharmacology

THE ACTIONS AND USES OF DRUGS

Sixth Edition

T. Z. Csáky, M.D.

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Preface

The unique feature of Cutting's Handbook is the presentation, in concise form, of the relationship between the chemical structure and the pharmacologic action of a large number of drugs. The wide acceptance of the previous editions by professionals and students fully justifies the need for such an approach.

In this new edition the basic structure of the book has remained unchanged. In the description of the drug-classes, those changes that were necessary because of alterations in basic concepts were made. An attempt was made to continue the custom of including new compounds even if these are still only experimental.

Thanks are due to several readers of the previous edition, especially Dr. Joseph Jerome, who, besides helping to update the previous edition was instrumental in securing the continuing cooperation of the U. S. Adopted Names Council. My wife rendered substantial assistance. The skillful technical contribution of Mrs. Virginia Crutcher is acknowledged.

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Contents

1.
The Sulfonamides

Paul Ehrlich in 1906 crystallized the hope of every chemotherapist since that time in the words "therapia sterilisans magna," by which he meant complete eradification of an infecting organism by a drug. Ehrlich before this had been working in immunotherapy, but now he created the concept of chemotherapy, meaning the treatment of infections by small, often synthetic, molecules, instead of larger protein antibodies.

Before Ehrlich only a handful of specific chemotherapeutic agents were known: aspidium, mercury, ipecac, quinine. At present, with the partial exception of viral infections, all the groups of infectious agents are at least accessible to chemotherapy.

The Ehrlich influence lasted until the 1920's and added atoxyl, arsphenamine, suramin, and bismuth to the therapeutic list. With these agents most protozoal infections became reasonably susceptible to treatment. Most importantly, it had been demonstrated that man might make drugs without precedent in nature.

Until the early 1930's it seemed that chemotherapy against bacteria was impossible, or at least too toxic for clinical use. However, when the sulfonamides were appreciated and exploited, modern chemotherapy became perhaps the most important field of therapy.

The sulfonamides were responsible for two major innovations: the effective treatment of bacterial infections, and the antimetabolite explanation of drug action. Even though now replaced for most uses by other drugs, they are of profound historical and theoretical interest, and the excitement of their discovery has not been forgotten.

1. History. a. Gelmo (1908) synthesized *p*-aminobenzenesulfonamide.

b. Heidelberger and Jacobs (1919) showed the antibacterial property of an azosulfonamide, but unfortunately the lead was not followed up.

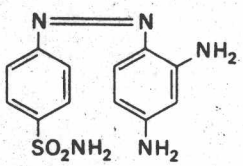
c. Domagk (1932) discovered the antibacterial property of Prontosil.

d. Trefuël, Trefuël, Nitti and Bovet (1935) showed that sulfanilamide was the active portion of Prontosil.

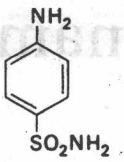
e. Colebrok and Kenny (1936) furnished clinical proof of the efficacy of Prontosil in puerperal fever.

f. Woods and Fildes (1940) showed that *p*-aminobenzoic acid (PABA) was an inhibitor of sulfanilamide.

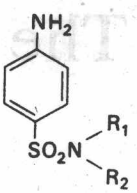
2. Chemistry. Prontosil, the earliest of the sulfonamides, is a diazo compound, one half of which is *p*-aminobenzenesulfonamide (sulfanilamide), the active moiety. Derivative sulfonamides are made by substitutions in the amide of the sulfonamide group.



Prontosil



sulfanilamide



derivatives

3. Action. a. In ordinary dosage, the sulfonamides exert inhibitory effects, largely bacteriostatic, on many microorganisms; the host assists by phagocytosis and immune mechanisms.

b. General effectiveness:

a'. Gram-positive bacteria: Most are susceptible: e.g., streptococci, staphylococci, pneumococci.

b'. Gram-negative bacteria. Many are no longer susceptible because of the development of resistant strains.

c'. Other susceptible microorganisms: Actinomyces, "large viruses" of trachoma and lymphogranuloma venereum.

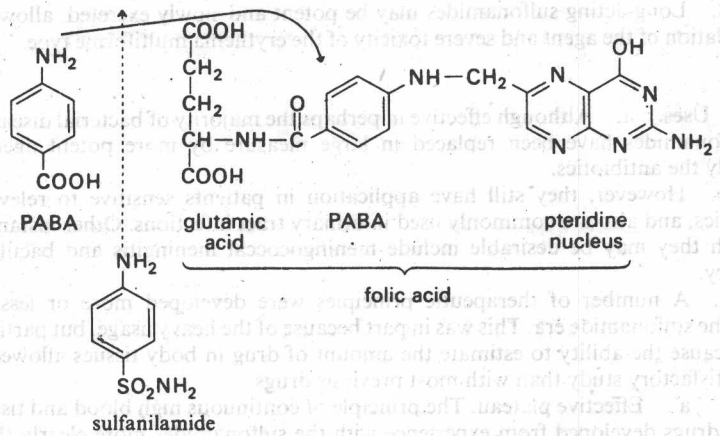
c. Different sulfonamides vary in effectiveness. Inside the bacterial cell, sulfanilamide is theoretically the most active member of the series as it resembles PABA most closely. However, sulfadiazine and others are more active in practice, possibly because of better penetration into the parasite.

A general comparison of in vivo effects at therapeutic dosage is shown in the following table (relative effectiveness varies to some extent with the infecting organism):

DRUG	RELATIVE EFFECTIVENESS
sulfapyridine	125
sulfathiazole	125
sulfadiazine	100
sulfamethazine	75
sulfamerazine	50
sulfisoxazole	50
sulfacetamide	25

4. Mechanism. a. Woods noted that sulfanilamide was inactive in the presence of pus or yeast; then that yeast contained PABA; and finally that sulfanilamide and PABA were competitive antagonists of each other. This led to the important thesis that substances with structural resemblances to each other might compete with each other, and that this could be a mechanism of action of drugs.

b. The competition between PABA and sulfanilamide is for incorporation into folic acid (or probably more accurately, for attachment to the enzyme which carries them into this incorporation). This mechanism is general for all the sulfonamides:



c. The basis for the selective action upon bacteria and not on higher cells probably lies in the following hypothesis: susceptible bacteria need PABA, as they are impermeable to folic acid, or use some other derivative of PABA than folic acid; therefore a block in the utilization of PABA is lethal. Nonsusceptible bacteria are probably permeable to folic acid and so may use it directly from the medium. Humans require premade folic acid-and therefore a lack of PABA is inconsequential.

d. Resistance to sulfonamides may involve increased production of PABA (gonococci).

5. Pharmacodynamics. a. Except for toxicity, sulfanilamide comes close to being an ideal drug as it is soluble, well absorbed, easily estimated, widely distributed in the body, and well excreted. Unfortunately, the more potent sulfonamides are less ideal.

b. The following are general characteristics for most members of the series: Absorption, alimentary or parenteral, rapid, in minutes; estimation, easy, by diazotization to colored compounds (Bratton, A. C., and Marshall, E. K. J. Biol. Chem., 128 : 537, 1939); distribution, widespread, with the water of the body, including penetration into the spinal fluid; metabolism, varying degrees of acetylation (of the para-NH_2), with some sulfonamides producing insoluble derivatives; excretion, moderately rapid, in 24 to 48 hours via the urine.

6. Toxicity. a. Most sulfonamides may produce mild toxic effects: nausea, dizziness.

b. Most also can produce severe sensitivity phenomena: dermatitis and rash, agranulocytosis, hepatitis.

c. Other manifestations are peculiar to certain sulfonamides. Thus, sulfanilamide may produce acidosis, cyanosis (met- or sulf-hemoglobinemia), and anemia; sulfapyridine and many others may produce renal damage and renal block by the insolubility of the parent compound or the acetyl derivative.

d. Long-acting sulfonamides may be potent and slowly excreted, allowing accumulation of the agent and severe toxicity of the erythema multiforme type.

7. Uses. a. Although effective in perhaps the majority of bacterial diseases, the sulfonamides have been replaced in large measure by more potent agents, primarily the antibiotics.

b. However, they still have application in patients sensitive to relevant antibiotics, and also are commonly used in urinary tract infections. Other instances in which they may be desirable include meningococcal meningitis and bacillary dysentery.

c. A number of therapeutic principles were developed more or less as part of the sulfonamide era. This was in part because of the heavy usage, but particularly because the ability to estimate the amount of drug in body tissues allowed a more satisfactory study than with most previous drugs.

a′. Effective plateau. The principle of continuous high blood and tissue level of drugs developed from experience with the sulfonamides more clearly than before.

b′. Initial and maintenance administration. The principle of a large initial dose to saturate to the desired therapeutic level, followed by maintenance doses at intervals which would maintain this level, although recognized before as with digitalis, became clearer because of the opportunity to follow blood levels.

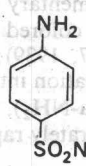
c′. Certain therapeutic principles special to the sulfonamides were also developed. Alkalinization of the urine was found to increase the solubility of most of the sulfonamides and their acetyl derivatives, and so to help prevent renal damage. Mixtures of sulfonamides were found in most instances to exert additive therapeutic effect with mutual solubility, again furnishing a means of limiting renal damage. The intravenous administration of sodium salts was found to establish a rapid initial saturation of the tissues at the desired level.

8. Preparations

a. Systemic sulfonamides: Scores of sulfonamides have been synthesized and a considerable number have come into clinical use. In this section the more prominent members that have been used to treat systemic infections are considered.

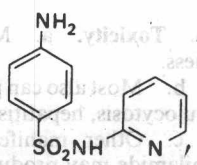
a′. Early preparations, largely obsolete

SULFANILAMIDE (Prontylin *)



After Prontosil, the earliest of the series; obsolete.

SULFAPYRIDINE (Dagenan, M & B 693, and others)



Greatly increased potency over sulfanilamide but both sulfapyridine and the acetyl derivative insoluble, giving renal damage; obsolete for general use, but used in dermatitis herpetiformis and other dermatological conditions.

Dose: 1 gm 4 times a day by mouth, reduced to 1 or 2 times a day.

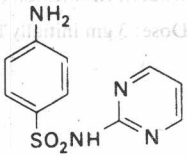
* Trademark: throughout the book limited to one or two common examples.

SULFATHIAZOLE (Thiazamide, and others)

Also potent, but toxicity common, especially to skin and marrow; obsolete.

b'. Short-acting preparations

SULFADIAZINE (Pyrimal, and others)

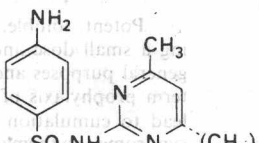


The standard general purpose sulfonamide, with which others are usually compared. Nearly as potent as sulfathiazole, but less toxic; serious reactions, i.e., blood dyscrasias and hepatitis, occur in about 0.1 % of patients.

Dose: 4 gm initially by mouth, then 1 gm every 4 hours for maintenance.

Sodium sulfadiazine, 0.5 to 4 gm intravenously in 5 % solution.

SULFAMERAZINE (Methylpyrimal; etc.) and SULFAMETHAZINE (Diazil; etc.)



The methyl and dimethyl derivatives of sulfadiazine, somewhat more slowly excreted.

Dose: As for sulfadiazine.

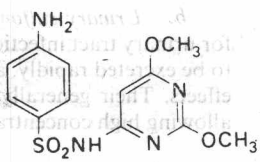
Trisulfapyrimidines (triple sulfonamides)

Combinations of equal parts of sulfadiazine, sulfamerazine and sulfamethazine.

Dose: as for sulfadiazine.

c'. Long-acting preparations

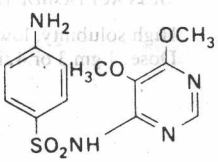
SULFADIMETHOXINE (Madribon)



Similar to sulfamethoxypyridazine but slowly converted into the favorably soluble glucuronide instead of the usual acetyl derivative. Cumulation may lead to severe toxicity, as for sulfamethoxypyridazine.

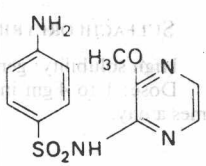
Dose: 2 gm by mouth (initial), then 1 gm daily.

SULFADOXINE (Fanzil)



Dose: 1 gm by mouth (single administration).

SULFALENE (Kelfizina)

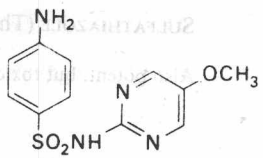


Extremely long acting. Used with pyrimethamine in resistant malaria.

Dose: 1 gm by mouth as a single dose under trial.

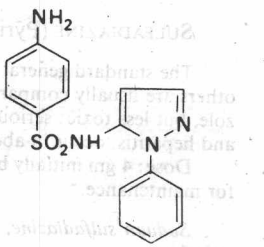
SULFAMETER (Sulla)

Dose: 0.5 gm by mouth twice on first day, then 0.5 gm daily.



SULFAPHENAZOLE (Sulfabid)

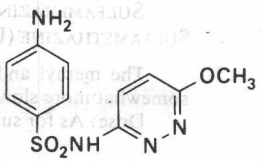
Dose: 3 gm initially by mouth, then 1 gm twice daily.



SULFAMETHOXYPYRIDAZINE (Kynex)

Potent, soluble, well absorbed, slowly excreted, allowing a small dose and infrequent administration. Used for general purposes and urinary tract infections; also in long term prophylaxis of rheumatic fever. Slow excretion may lead to cumulation and severe toxicity; Stevens-Johnson syndrome (erythema multiforme) reported.

Dose: 0.5 gm 2 times a day by mouth.



Acetyl sulfamethoxypyridazine (Kynex Acetyl)

Tasteless, for pediatric use; also adjunct to sulfones in leprosy.

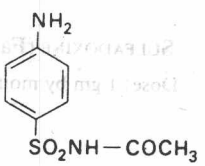
Dose: Same as for sulfamethoxypyridazine.

b. Urinary sulfonamides: A number of sulfonamides are used particularly for urinary tract infections. They tend to be weaker than the systemic sulfonamides, to be excreted rapidly, and to produce blood levels too low for satisfactory systemic effects. Their generally high solubility reduces the chance of renal damage while allowing high concentration in the urinary tract.

SULFACETAMIDE (Sulamyd)

High solubility, low toxicity.

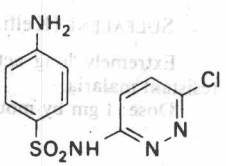
Dose: 1 gm 3 or 4 times a day by mouth.



SULFACHLORPYRIDAZINE (Sonilyn)

High solubility; generally resembles sulfisoxazole.

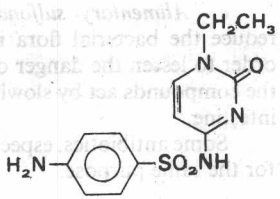
Dose: 1 to 4 gm initially by mouth, then 1 gm 3 to 6 times a day.



SULFACYTINE (Renoquid)

Short acting, rapidly excreted.

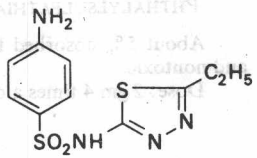
Dose: 250 mg 4 times a day by mouth.



SULFAETHIDOLE (Sul-spansion)

Excreted rapidly and therefore given in sustained-release preparations.

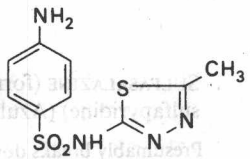
Dose: 1 to 2 gm by mouth 2 times a day.



SULFAMETHIZOLE (Thiosulfil)

Good solubility, fair potency.

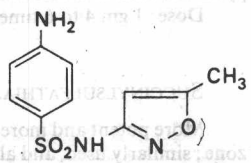
Dose: 0.25 to 0.5 gm 4 to 6 times a day by mouth.



SULFAMETHOXAZOLE (Gantanol)

Less well absorbed and more slowly excreted than sulfisoxazole. Rare nausea and vomiting.

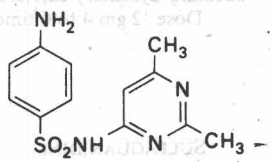
Dose: 2 gm initially by mouth, then 1 gm every 12 hours.



SULFISOMIDINE (Elkosin)

High solubility, low toxicity.

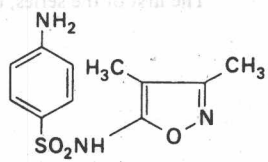
Dose: 1 gm 3 times a day by mouth.



SULFISOXAZOLE (Gantrisin)

Popular urinary antiseptic; highly soluble and unlikely to produce crystalluria; occasional sensitivity manifestations, especially of skin.

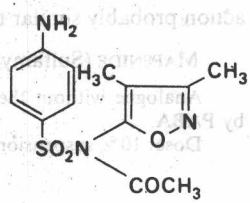
Dose: 4 gm by mouth (initial), then 1 to 2 gm every 4 hours.



Sulfisoxazole diolamine

Acetylsulfisoxazole

Split to sulfisoxazole in the intestine; may be preferred for administration in emulsions to children.



c. Alimentary sulfonamides: Poorly absorbed sulfonamides are used to reduce the bacterial flora in the bowel before abdominal surgical operations in order to lessen the danger of peritoneal contamination. Except for sulfaguanidine, the compounds act by slowly breaking down to sulfathiazole or sulfapyridine in the intestine.

Some antibiotics, especially neomycin, are used, alone or with the sulfonamides, for the same purpose.

PHTHALYLSULFATHIAZOLE (Sulfathalidine)

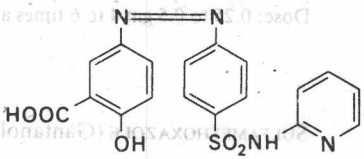
About 5% absorbed from the bowel; relatively effective and nontoxic.

Dose: 2 gm 4 times a day by mouth.

SULFASALAZINE (formerly Salicylazosulfapyridine) (Azulfidine and others)

Presumably breaks down slowly to sulfapyridine; used in ulcerative colitis.

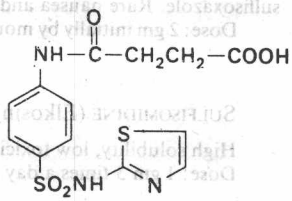
Dose: 1 gm 4 to 6 times daily by mouth.



SUCCINYLSULFATHIAZOLE (Sulfasuxidine)

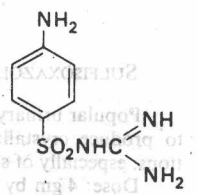
More potent and more toxic than phthalylsulfathiazone; similarly used, and also in ulcerative colitis and in bacillary dysentery carriers.

Dose: 2 gm 4 to 6 times a day by mouth.



SULFAGUANIDINE

The first of the series, obsolete.

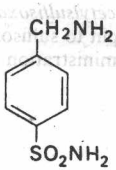


d. Related sulfonamides: Para-amino group not present. Mechanism of action probably similar to sulfonamides.

MAFENIDE (Sulfamylon)

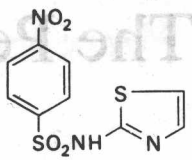
Analogue without the para-amino group; is not inactivated by PABA.

Dose: 10% suspension locally for burn and wound antisepsis.



PARA-NITROSULFATHIAZOLE (Nisulfazole)

Used in ulcerative colitis.
Dose: 10 ml of a 10% suspension by rectum.



SUMMARY: THE SULFONAMIDES

TYPE	*ACTION AND MECHANISM*	*TOXICITY*	*USE*	*EXAMPLES*
Sulfonamides, systemic	Bacteriostatic gram-pos. gram-neg. Block formation of folic acid by competition with PABA	Sensitization, crystalluria, erythema multiforme	Meningococcal meningitis bacillary dysentery	Sulfadiazine
Sulfonamides, urinary	Same	Sensitization	Urinary tract infection	Sulfisoxazole
Sulfonamides, alimentary	Same	Minor	Bacillary dysentery Surgical preparation	Succinyl-sulfathiazole
Sulfonamides, other	Probably similar	Minor	Local burns, wounds	Mafenide

Reviews

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