Technical Papers

An Intestinal Antiseptic: 2-Sulfanilamido-5-Carboxythiazole[1]

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The synthesis of 2-sulfanilamido-5-carboxythiazole was first described in the literature by Backer and DeJonge (*1*), but no information concerning its chemical, pharmacological, or antibacterial properties was given. Like sulfaguanidine, succinylsulfathiazole, and phthalylsulfathiazole, 2-sulfanilamido-5-carboxythiazole is poorly absorbed from the gastrointestinal tract and possesses high antibacterial activity.

Chemistry. 2-sulfanilamido-5-carboxythiazole is a white, crystalline material and is stable in solid form. Samples over two years old have shown no deterioration. Analyses of the thoroughly dried compound give, within experimental limits, theoretical values for C, H, and N. When heated, the substance decomposes with effervescence between 200° and 220° C., depending on the rate of heating and the temperature of the bath when the melting-point tube is inserted. The compound is a fairly strong acid, liberating carbon dioxide when dissolved in sodium bicarbonate solution. Its solubility in water at room temperature (23°–25° C.) is approximately 40 mg. per cent. The pH of the saturated solution is 3.2. The solubilities in water of the mono and the disodium salts are greater than 30 per cent, the pH being 5.4 and 8.5, respectively. The sodium salt of the acetyl derivative has a solubility of approximately 8 per cent, and the pH of the saturated solution is 5.4.

The high solubility of the sodium salts of 2-sulfanilamido-5-carboxythiazole gives a chemical basis for the concentrations of the drug in solution that can be maintained in the intestinal tract. Any 2-sulfanilamido-5-carboxythiazole which is absorbed and which may be partially acetylated in the body will be freely soluble in the body fluids. This suggests strongly that there is little danger of deposition of crystals of the drug or its acetyl derivative in the kidneys or urinary tract, and the expectation has been borne out in all of the experimental work to date.

In vitro studies. The *in vitro* bacteriostatic activity of 2-sulfonilamido-5-carboxythiazole was tested against streptococcus, pneumococcus, and staphylococcus and against members of the colon-typhoid dysentery group, including *Vibrio cholerae*. Results are shown in Table 1. Data obtained with the more commonly known sulfonamides are included.

TABLE 1

COMPARISON OF BACTERIOSTATIC ACTIVITY OF 2-SULFANILAMIDO-5-CARBOXYTHIAZOLE WITH OTHER SULFONAMIDES*

	Lowest concentration (mg. per cent) at which stasis was exhibited at 72 hours					
	SA	SP	ST	SD	SG	SC
Streptococcus (C203)	10.0	5.0	2.5	10.0	10.0	10.0
Pneumococcus (SVI)	2.5	1.25	0.3	2.5	1.25	2.5
Staphylococcus aureus (Barlow)	1280		2.5	5.0		>160
Escherichia coli	20.0	5.0	0.6	0.6	10.0	5.0
Aerobacter aerogenes	80.0	5.0	2.5	5.0	160	10.0
Salmonella enteritidis	>80.0	10.0	2.5	2.5	>80.0	20.0
Shigella dysenteriae (Shiga)	2.5	0.15	0.15	0.15	2.5	0.6
Shigella sonnei	20.0	1.25	0.3	0.6	10.0	2.5
Shigella paradysenteriae (Flexner I)	40.0	0.6	0.6	0.6	20.0	0.6
Shigella paradysenteriae (Flexner II)	40.0	2.5	0.6	1.25	20.0	2.5
Shigella paradysenteriae (Flexner III)	2.5	2.5	0.3	0.3	10.0	2.5
Vibrio cholerae	10.0	1.25	0.15	0.6	20.0	5.0

* SA = Sulfanilamide, SP = sulfapyridine, ST = sulfathiazole, SD = sulfadiazine, SG = sulfaguanidine, SC = 2-sulfanilamido-5-carboxythiazole.

It was found that 2-sulfanilamido-5-carboxythiazole possessed as much activity against streptococcus as did sulfanilamide, sulfadiazine, and sulfaguanidine. Against pneumococcus, it again showed comparable activity with sulfanilamide and sulfadiazine, being only slightly less active than sulfapyridine and sulfaguanidine. It proved more active against staphylococcus than sulfanilamide, while sulfathiazole was the most active of the compounds tested. It showed appreciable activity against the enteric group of organisms, being in general more active than sulfanilamide and sulfaguanidine, and in some instances equal to sulfapyridine, sulfathiazole, and sulfadiazine.

[1] The writer acknowledges the assistance of E. R. Bockstahler, H. E. Faith, H. J. Florestano, J. F. Kennedy, and H. E. Martin, Pitman-Moore Company, Indianapolis, Indiana.

In vivo studies. Acute toxicity of 2-sulfanilamido-5-carboxythiazole in mice gave the following results: by oral administration, LD_{50}, 8.0 grams/kg.; intraperitoneal, LD_{50}, 5.0–6.0 grams/kg.; subcutaneous, LD_{50}, 8.0 grams/kg. The chronic toxicity studied in mice, rabbits, and dogs was found to be much less than that of the readily absorbed sulfonamides and sulfaguanidine and comparable with succinylsulfathiazole.

Studies on the absorption following oral administration were carried out in mice, rabbits, dogs, and men. Blood levels obtained in all species were low (e.g. in man given 0.25 grams/kg./day for five days, the maximum blood level was less than 1.0 mg. per cent).

Absorption and excretion studies in man revealed that from 3 to 11 per cent of the 2-sulfanilamido-5-carboxythiazole administered orally was excreted in the urine, the average being 6.1 per cent.

The effect of the compound on reducing the number of coli in the feces of dogs and man was very striking. Comparison of the data with those of Poth, *et al.* (*3*) indicates that 2-sulfanilamido-5-carboxythiazole reduces the number of coli more rapidly and at a lower dose level than either succinylsulfathiazole or phthalylsulfathiazole. In a study of more than 200 patients on succinylsulfathiazole therapy, Poth and his co-workers found that 38 per cent showed less than 1,000 *E. coli*/gram of wet feces within three days of treatment, and that 79 per cent had less than this number within five days of treatment and 93 per cent within seven days. Poth explained that the remaining 7 per cent failed to respond to therapy within seven days because of some condition interfering with the action of the drug. The dosage used by Poth consisted of 0.25 gram/kg. of succinylsulfathiazole as an initial dose, followed in four hours by 0.25 gram/kg. daily, divided in six equal amounts and administered at four-hour intervals. Although the number of subjects on 2-sulfanilamido-5-carboxythiazole was small, it is worthy to note that the most refractory case studied had less than 1,000 coli/gram of feces within 48 hours of treatment at the same dosage employed by Poth. One subject, given one-half the dosage, showed less than 10 coli/gram of feces within 48 hours of treatment. With two subjects on 0.25 gram/kg. daily, omitting the initial dose of 0.25 gram/kg., a count of less than 1,000 coli/gram of feces was obtained within the first 24 hours of therapy. At the end of the second day, both counts were below 10 coli/gram of feces. Thus, in each of the four instances where 2-sulfanilamido-5-carboxythiazole was administered in doses either equal to or decidedly less than that employed by Poth for succinylsulfathiazole, coli counts of less than 1,000/gram of wet feces resulted within two days of treatment.

In an independent clinical study of the compound, Harris and Finland (*2*) report findings that are in general agreement with these. They used the drug in treating cases of bacillary dysentery and state that, in the amounts given, it is poorly absorbed and that, as far as could be determined it is nontoxic. They found the drug to be effective in the cases of dysentery studied and state that it may deserve a place with the other drugs used in enteric infections and in bowel surgery.

Extensive clinical trials at a number of medical centers are now in progress which will establish the value of 2-sulfanilamido-5-carboxythiazole relative to that of other drugs used for intestinal antisepsis.

References

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Pectoral Girdles *vs.* Hyobranchia in the Snake Genera *Liotyphlops* and *Anomalepis*

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The Serpentes have always been considered to differ from all other reptiles in having lost the pectoral girdle completely. Recently, however, Dunn and Tihen (*1*) reported the discovery of a shoulder girdle in a primitive burrowing snake, *Liotyphlops albirostris*. This report seems to warrant further investigation before the interpretation of this structure can be accepted or rejected.

The specimens studied are, in part, the same as those used by Dunn and Tihen. Two specimens of *Liotyphlops albirostris* stained with alizarin red and cleared in glycerine were obtained from Dr. J. A. Tihen. Mr. K. P. Schmidt provided a stained specimen of *Anomalepis dentatus*. Finally, one specimen of *Anomalepis aspinosus,* used for gross dissection, was loaned by Mr. A. Loveridge. The writer is greatly indebted to these authorities for providing the necessary material.

Anomalepis, which is considered a close relative of *Liotyphlops,* possesses the same structure that Dunn and Tihen described in *Liotyphlops*. It is here considered valid, therefore, to apply findings in the