

Ocular Absorption of Sulfonamide Derivatives After Local Application.*

SHIH-YI P'AN. (Introduced by Hamilton H. Anderson.)

From the Department of Pharmacology, Peiping Union Medical College, Peking, China.

It has been reported previously^{1, 2} that sulfanilamide and sulfapyridine after local application to the eyes of experimental animals are absorbed in greater amounts by ocular tissues and fluids than occurs when these agents are administered orally.³⁻⁷ The ocular absorption of sulfathiazole has recently been studied by Bellows and Chinn.⁸ Dogs given 0.2 g per kg of the drug, which was dissolved in HCl before administration, after 4 hours developed blood concentrations of 7.4 mg %. The amounts of sulfathiazole found in ocular tissues and fluids were: sclera 10.4, conjunctiva 8.4, chorioretinal layers 4.9, cornea 2.0, vitreous humor 0.9, aqueous humor 0.4, and lens 0 mg %. When an aqueous suspension of a similar dose of sulfathiazole was given orally the concentrations were considerably lower: blood 1.7, conjunctiva 2.9, chorioretinal layers 1.7, aqueous humor 0.3, vitreous humor 0.2 and lens and cornea 0 mg %. Similar results have been reported on cats by Scheie and Souders,⁹ who found that a very small amount of sulfathiazole diffuses into the aqueous humor as compared with the blood concentration. In addition they have observed that sulfadiazine, like sulfanilamide, penetrates into the aqueous humor when given orally. Turkell and Wilhelm¹⁰ have shown that

* Sulfaguanidine and sulfadiazine were supplied by the Lederle Laboratories, Pearl River, N.Y.; N⁴-nicotinylsulfanilamide by the Lilly Laboratories, Indianapolis, Ind.; N¹-nicotinylsulfanilamide was prepared by Dr. Chas. H. Ch'eng of our laboratory, and N¹,N⁴-dinicotinylsulfanilamide by Dr. Troy Daniels, University of California, College of Pharmacy, San Francisco, Calif.

¹ P'an, S. Y., *Proc. Soc. Exp. Biol. and Med.*, 1941, **46**, 31.

² P'an, S. Y., *J. Pharm. and Exp. Therap.*, 1941, **72**, 31.

³ Rumbo, V. C., *Am. J. Ophthalm.*, 1938, **21**, 739.

⁴ Bellows, J. G., and Chinn, H., *J. A. M. A.*, 1939, **112**, 2023.

⁵ Mengel, W. G., *Arch. Ophthalm.*, 1939, **22**, 406.

⁶ Luo, T. H., and P'an, S. Y., *Chin. M. J.*, 1940, **58**, 167.

⁷ Meyer, K., Bloch, H. S., and Chamberlain, W. P., Jr., *Am. J. Ophthalm.*, 1941, **24**, 60.

⁸ Bellows, J. G., and Chinn, H., *Arch. Ophthalm.*, 1941, **25**, 294.

⁹ Scheie, H. G., and Souders, B. F., *Arch. Ophthalm.*, 1941, **25**, 1025.

¹⁰ Turkell, J., and Wilhelm, S. F., *Proc. Soc. Exp. Biol. and Med.*, 1941, **47**, 97.

sulfathiazole was secreted in tears in amounts far less than in the blood after oral use.

Since sulfanilamide and related agents have been used in the therapy of ocular diseases it was believed desirable to compare the absorptive rates of 8 sulfonamide derivatives after local application to the eyes of rabbits. The technic employed has been described elsewhere.¹ For N⁴-nicotinylsulfanilamide and N¹,N⁴-dinicotinylsulfanilamide a method not previously described has been used.[†]

Table I summarizes the results of the present series of experiments together with those obtained with sulfanilamide and sulfapyridine as previously reported.^{1, 2} The N⁴-nicotinylsulfanilamide was not included in the table because none of it was found in any of the ocular tissues or fluids or blood after its local application to the eyes of 6 rabbits. It may be seen that the absorption of N¹-nicotinylsulfanilamide and N¹,N⁴-dinicotinylsulfanilamide was comparable to that of sulfanilamide and sulfapyridine. The concentrations of sulfathiazole, sulfaguanidine and sulfadiazine in the cornea of rabbits locally treated with each drug were definitely higher, and of the conjunctiva were equal or above those found in these tissues after oral administration of reasonable doses of the 3 derivatives. Local application of these 3 agents resulted in ineffective concentrations developing in the lens, sclera, chorioretinal layers, aqueous humor and vitreous humor as well as in the blood. No evidence of chemosis or other signs of irritation to ocular tissues were noted after the application of any one of these derivatives. Six or more eyes were treated with each sulfonamide derivative reported in this experiment.

To be of value in the therapy of localized ocular infections, one would assume that therapeutically effective tissue concentrations are needed. Local application of powdered sulfonamides to the normal rabbit's eye for 60 minutes resulted in the accumulation of significant amounts of all agents in the conjunctiva and cornea, except after

† Sodium hydroxide instead of HCl was used for hydrolysis at the suggestion of Dr. Jack Finnegan, University of California Medical School, San Francisco. Ocular tissues were mixed with an appropriate amount of 85% alcohol so that each cc contained 20 mg of tissue. The mixture was filtered and 2 cc of the filtrate was pipetted into 17 × 150 mm test tubes graduated at 10 cc. One cc of 2N NaOH and 3 cc of water were added and the tube was placed in a bath of boiling water for 2½ hours. The mixture was neutralized to phenolphthalein with N HCl and diluted with distilled water to 10 cc. After cooling, 2 cc of 0.025% NaNO₂ was added and 3 minutes later 5 cc of 0.4% dimethyl- α -naphthylamine in 95% alcohol was added and the solution was compared with an appropriate standard in a Klett-Summerson photoelectric colorimeter using filter No. 54. For blood, 0.1 cc was added to 5 cc of 85% alcohol and the mixture was filtered and 2 cc of the filtrate was treated in a similar manner.

TABLE I.

Amounts of Sulfonamide Derivatives Found After Local Application (in mg per 100 g or cc).

	Conjunctiva	Cornea	Sclera	Lens	Chorio-retinal layers	Aqueous humor	Vitreous humor	Blood [†]
R ₁ =H R ₄ =H Sulfanilamide*	89.8±14.0	185.4±15.2	23.3±4.6	8.7±1.8	12.3±1.2	54.8±5.3	1.1±0.2	0
R ₁ = R ₄ =H Sulfapyridine**	47.1±11.2	30.5±6.0	10.9±3.6	2.4±0.8	0	4.7±1.2	0	0
R ₁ = R ₄ =H Sulfathiazole	8.9±1.7	23.5±1.9	3.2±0.5	0	0	2.1±0.3	0.1±0.1	0
R ₁ = R ₄ =H Sulfaguanidine	4.9±1.0	11.5±2.5	0.9±0.1	0.4±0.2	0	0.8±0.1	0.2±0.2	0
R ₁ = R ₄ =H Sulfadiazine	4.9±0.7	9.4±0.8	1.6±0.3	0	0	2.2±0.5	0	0
R ₁ = R ₄ =H N ¹ -nicotinyln-sulfanilamide	10.7±2.9	140.5±15.6	13.0±3.1	4.6±0.9	9.2±1.8	37.7±10.5	0.5±0.2	0
R ₁ , R ₄ = R ₄ =H N ¹ , N ⁴ -dinicotinyln-sulfanilamide	8.6±1.7	61.6±8.8	6.8±1.8	0.3±0.3	0.3±0.3	7.2±1.6	0	0

†Effective blood concentrations for systemic activity are: sulfanilamide 10 mg%, sulfapyridine, sulfathiazole, sulfaguanidine and sulfadiazine 5 mg%.

*See PROC. SOC. EXP. BIOL. AND MED., 1941, 46, 31.

**See J. Pharm. and Exp. Therap., 1941, 72, 31.

N⁴-nicotinyln-sulfanilamide. Sulfanilamide and N¹-nicotinyln-sulfanilamide are absorbed in effective amounts by all tissues and fluids except the vitreous humor. Sulfapyridine and N¹, N⁴-dinicotinyln-sulfanilamide are found in therapeutic concentrations in the conjunctiva, cornea, sclera, and aqueous humor. The finding that sulfathiazole, sulfaguanidine and sulfadiazine were present in effective concentrations only in the conjunctiva and cornea indicates that they were slowly absorbed by other ocular tissues and fluids and possibly remained in the conjunctiva and cornea for a comparatively longer time. It may, therefore, point to preference for these 3 drugs when ocular infections are localized to the conjunctiva and cornea.