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Chemotherapeutic Evaluation of N^4-n-Acylsulfanilylhydroxamides.

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The antienzymatic theory of the mode of action of sulfanilamide and related compounds, as specifically represented by their inactivation of catalase, is finding increasing experimental support.[1-10] Such action, however, is chiefly predicated on the formation of intermediate products of oxidation of the amino group, as represented by p-hydroxylaminophenylsulfonamide. The present study deals with a new series of sulfanilamide derivatives in which the amide group has been oxidized and the amino group blocked by acylation. In view of the fact that such blockage has destroyed *in vitro* anticatalase activity[3] and to a considerable extent the therapeutic activity of previously examined derivatives, it follows that the anticatalase activities of N^4-n-valeryl-, N^4-n-caproyl- and N^4-n-heptanoylsulfanilylhydroxamide* [11] depends upon their oxidized amide groups.

Bearing in mind the fact that the hydroxamide group is already present and does not have to be formed by the bacteria, these compounds should possess powerful anticatalase and bacteriostatic properties, and because of these properties, superior therapeutic activity unless changed radically and quickly by the host. A study of the first possibility will be reported by Main, Shinn, and Mellon;[12] the study of the second is reported in the present paper.

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* Synthesized and donated to us by Sharp and Dohme, Glenolden, Penn.

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TABLE I.
Streptococcic (Strain C 203) Infection of Mice (1,000 Fatal Doses).

Treatment	No. of mice	No. of deaths daily during 21 days									No. of Survivors	% Survivors
		1	2	3	4	5	6	7	8	9-21		
None	75	63	7	2	2					1	None	None
Sulfanilamide	62	3	1	1		1				10	46	74
Sulfapyridine	62	1								11	50	81
N⁴-n-Valerylsulfanilylhydroxamide	76	1	1		2	1		1		11	59	78
N⁴-n-Caproylsulfanilylhydroxamide	79	4	2					3	3	7	60	76
N⁴-n-Heptanoylsulfanilylhydroxamide	78	7	1	1		1	3		1	6	58	74

Infection: 0.5 cc of a 10^{-4} broth dilution of an 18-hour broth culture intraperitoneally (1,000 fatal doses).
Treatment: 10 mg of drug freshly suspended in 0.2 cc of 15% gum acacia orally 3 hours after infection, then once daily for 3 successive days (total 40 mg).

TABLE II.
Streptococcic (Strain Richards) Infection of Mice (1,000 Fatal Doses).

Treatment	No. of mice	No. of deaths daily during 21 days									No. of Survivors	% Survivors
		1	2	3	4	5	6	7	8	9-21		
None	20	14	5	1							None	None
Sulfanilamide	20		1		3	2	1	1		3	9	45
Sulfapyridine	20	1			1	1	2	1			14	70
N⁴-n-Valerylsulfanilylhydroxamide	20		1		2		1	2	1	4	9	45
N⁴-n-Caproylsulfanilylhydroxamide	39				4	3	6		4	6	16	41
N⁴-n-Heptanoylsulfanilylhydroxamide	20				2	3	1	1	1	1	11	55

Infection: 0.5 cc of a 10^{-6} broth dilution of an 18-hour broth culture intraperitoneally (1,000 fatal doses).
Treatment: 10 mg of drug freshly suspended in 0.2 cc of 15% gum acacia orally 3, 22 and 46 hours after infection (total 30 mg).

TABLE III.
Type II Pneumococcic (Strain Binda) Infection of Mice (100-1,000 Fatal Doses).

Treatment	No. of mice	No. of deaths daily during 21 days									No. of Survivors	% Survivors
		1	2	3	4	5	6	7	8	9-21		
None	40	6	26	7	1						None	None
Sulfanilamide	35			4	3	3	7	6	3	3	6	17
Sulfapyridine	34		1	1			6	7	3		16	47
N^4-n-Valerylsulfanilylhydroxamide	40		2	2	4	14	10	2	1	1	4	10
N^4-n-Caproylsulfanilylhydroxamide	39			1	5	13	8	3	2	3	3	8
N^4-n-Heptanoylsulfanilylhydroxamide	39		3	2	15	13	4	2			None	None

Infection: 0.5 cc of a 10^{-6} broth dilution of an 18-hour broth culture of type II subcutaneously (100-1,000 fatal doses).
Treatment: 20 mg of drug freshly suspended in 0.2 cc of 15% gum acacia orally 3 hours after infection, then once daily for 5 successive days (total 120 mg).

Mice infected with 2 strains of hemolytic streptococci and one strain of Type II pneumococci were treated 3 hours after infection as indicated in Tables I, II, and III. Any mouse which failed to show the infecting organism in the blood or peritoneal cavity at death was excluded from the experiment. The ratio of infection to treatment was purposely adjusted so that one-half to three-quarters of the sulfanilamide- or sulfapyridine-treated mice died. In this way better comparative values are obtained than with optimum treatment. Such values may also have greater clinical significance because of the tendency of many clinicians to cut sulfonamide medication following the first signs of improvement in order to minimize objectionable side reactions.

Reference to Tables I, II and III shows that the N^4-acylsulfanilylhydroxamides are approximately equal to sulfanilamide in saving mice with hemolytic streptococcic or Type II pneumococcic sepsis.

Although the fate of the sulfonhydroxamide group cannot be followed in the body at present, all 3 compounds reduce hot Benedict reagent and cold ammonical silver nitrate readily. They also undergo deacylation to the extent that mice given 50 mg orally show approximately 10 mg % of diazotizable material, calculated as sulfanilamide, in the blood 2 hours later.

Conclusion. N^4-n-valeryl-, N^4-n-caproyl-, and N^4-n-heptanoylsulfanilylhydroxamide possess approximately the same therapeutic activity as sulfanilamide against sepsis in mice produced by 2 strains of hemolytic streptococci and one strain of Type II pneumococci.