SHIGELLA PARADYSENTERIAE INFECTION IN MICE

TREATMENT WITH SULFAGUANIDINE AND SULFACETIMIDE (SULAMYD)

MERLIN L. COOPER, M.D., AND HELEN M. KELLER
CINCINNATI, OHIO

IN PREVIOUS publications[1, 2] we have presented data concerning the therapeutic value of various sulfonamide drugs in the treatment of mice experimentally infected with *S. paradysenteriae*. The sulfonamide drugs tested were sulfathiazole, sulfapyridine, sulfanilamide, and sulfamethylthiazole. The first two were more effective and sulfanilamide was the least effective.

The purpose of this report is to present additional information regarding the therapeutic value of two sulfonamide compounds which have become available more recently; namely, sulfaguanidine* and sulfacetimide† (sulamyd). The technique used was the same as that reported in the previous publications. Groups of ten mice were injected intraperitoneally with 1, 10, 100, and 1,000 minimum fatal doses of culture suspended in 3 per cent mucin. One minimum fatal dose contained approximately 8,000 bacteria. Three hours after injection of the culture each mouse was given one dose of the sulfonamide compound by stomach tube. All control mice died when injected with one minimum fatal dose of culture and not treated with the drug. Of the control mice injected with one-tenth of a minimum fatal dose of culture and not treated with the drug, 60 per cent died.

Data in Tables I and II indicate that when Flexner and Sonne types of *S. paradysenteriae* were used, one dose of 10 mg. of either sulfaguanidine or sulfacetimide was necessary to give therapeutic results comparable to those obtained with 1 mg. of either sulfathiazole or sulfapyridine. These doses were the minimum effective doses.

The blood levels obtained one hour after administration of these minimum effective doses of the sulfonamide compounds were quite different. In Table III it may be seen that 10 mg. of sulfaguanidine and 10 mg. of sulfacetimide, respectively, gave blood levels of 1.8 mg. per cent and 22.3 mg. per cent. Three hours after the single dose of these drugs all blood levels were less than 1 mg. per cent. It is interesting that here are two sulfonamide compounds equally efficient in the treatment of mice, experimentally infected with *S. paradysenteriae*, at a time in the course of their infection when they have an overwhelming septicemia,[2] the one drug, sulfaguanidine, giving a low blood level of 1.8 mg. per cent and the other, sulfacetimide, giving a high

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.

*Supplied by Lederle Laboratories.

†Supplied by Schering Corporation.

blood level of 22.3 mg. per cent. In a previous study[2] 1 mg. of sulfathiazole, the minimum effective dose, was found to give a blood level of 2.4 mg. per cent.

TABLE I

SHIGELLA PARADYSENTERIAE OF FLEXNER: MORTALITY AMONG MICE GIVEN SULFONAMIDES BY STOMACH TUBE THREE HOURS AFTER INJECTION OF CULTURE AND MUCIN

MINIMUM FATAL DOSES	SULFATHIAZOLE (1 MG.)	SULFAPYRIDINE (1 MG.)	SULFANILAMIDE (1 MG.)	SULFAGUANIDINE (5 MG.)	SULFAGUANIDINE (10 MG.)	SULFACETIMIDE (10 MG.)
1	0*	0	2	2	1	0
10	2	0	6	5	1	2
100	4	6	9	6	7	3
1,000	10	10	10	10		10

Each of forty control mice was given 1 minimum fatal dose and all died.
*Ten mice in each group.

TABLE II

SHIGELLA PARADYSENTERIAE OF SONNE: MORTALITY AMONG MICE GIVEN SULFONAMIDES BY STOMACH TUBE THREE HOURS AFTER INJECTION OF CULTURE AND MUCIN

MINIMUM FATAL DOSES	SULFATHIAZOLE (1 MG.)	SULFAPYRIDINE (1 MG.)	SULFANILAMIDE (2 MG.)	SULFAGUANIDINE (10 MG.)	SULFACETIMIDE (10 MG.)
1	1*	1	2	2	2
10	5	4	7	3	3
100	6	6	10	9	9
1,000	6	7	10	10	-
10,000	10	10	10	-	-

Each of forty control mice was given 1 minimum fatal dosage; all died.
*Ten mice in each group.

TABLE III

BLOOD DRUG LEVELS IN MICE*

DOSE (MG.)	SULFAGUANIDINE		SULFACETIMIDE	
	1 HR. (MG. %)	3 HR. (MG. %)	1 HR. (MG. %)	3 HR. (MG. %)
2	--	----	3.8	Less than 1
5	1.0	Less than 1	11.2	Less than 1
8	1.4	Less than 1	---	----
10	1.8	Less than 1	22.3	Less than 1
12	1.1	Less than 1	---	----
20	1.8	Less than 1	---	----
40	3.0	Less than 1	---	----

*Pooled blood from two mice used for each determination.

Additional information concerning blood levels following the administration of various amounts of the two newer sulfonamides may be found in Table III. Note that large doses of sulfaguanidine gave only low blood levels, as would be expected, while sulfacetimide gave high levels.

Such marked differences in blood levels associated with effective doses of two sulfonamides seem to indicate that a sulfonamide poorly absorbed

and giving low blood levels may be quite as effective as another sulfonamide readily absorbed and giving high blood levels.

CONCLUSIONS

In the treatment of mice experimentally infected with *S. paradysenteriae,* a single minimum effective dose of 10 mg. of either sulfaguanidine or sulfacetimide (sulamyd) gave therapeutic results comparable to those obtained with a single minimum effective dose of 1 mg. of sulfathiazole or sulfapyridine.

These effective doses of sulfaguanidine and sulfacetimide (sulamyd) gave blood levels of 1.8 mg. per cent and 22.3 mg. per cent, respectively.

Wide variations in blood levels were found following administration of effective doses of sulfonamide compounds. This is especially interesting in view of the fact that the infected mice had overwhelming septicemias at the time the drugs were administered by mouth.

REFERENCES

1. Cooper, Merlin L., and Keller, Helen M.: Proc. Soc. Exper. Biol. & Med. **45**: 111, 1940.
2. Cooper, Merlin L., and Keller, Helen M.: J. PEDIAT. **18**: 458, 1941.