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Research Article

THE ABSORPTION AND EXCRETION OF STREPTOMYCIN IN HUMAN CHRONIC TYPHOID CARRIERS

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Streptomycin,[1] an antibiotic agent produced by the growth of *Actinomyces griseus,* has been shown to inhibit the growth of gram negative bacilli both *in vitro* (1 to 5) and in animals (2, 3, 6 to 9). Preliminary data on the absorption and excretion of this drug were obtained in a patient suffering from acute bacterial endocarditis due to *Pseudomonas aeruginosa,* the first human patient treated with streptomycin (10). The data indicated that it was possible to attain levels of the drug in the blood in the range of sensitivity of gram-negative bacilli of this antibiotic agent and justified the performance of more detailed studies of absorption and excretion of streptomycin.

Chronic typhoid carriers were selected as subjects for this study for several reasons; they were as relatively "normal" individuals as could be found in the population of the hospital and, in addition, provided an opportunity to study the effect of streptomycin on the typhoid carrier state.

METHOD OF STUDY

Four male chronic typhoid carriers, under the jurisdiction of the Department of Health of the City of New York, were admitted to the First Medical Division of Bellevue Hospital. These individuals were known to have had consistently positive cultures of typhoid bacilli in their stools without exception for at least 2 years. Following admission, a medical history was obtained and a physical examination was performed. The following control measurements in relation to this study were made: complete blood count, urinalysis, erythrocyte sedimentation rate (Westegren method), blood urea nitrogen (11), cephalin flocculation test (12), icteric index, and electrocardiogram. In addition to the tests performed in relation to drug absorption and excretion, the following measurements were made in relation to the typhoid carrier state. These included urine and stool cultures on MacConkey medium, Bacto S. S. Agar, and Wilson-Blair medium. The typhoid bacilli were typed according to the bacteriophage method of Craigie and Yen (13). The urine cultures were performed prior to therapy and repeated twice on successive days. Stool cultures were performed prior to therapy and daily thereafter, the last specimen being taken 15 hours after therapy was discontinued. The sensitivity of the strains of typhoid bacilli were determined by the agar plate method.

An intracutaneous skin test on the flexor aspect of the right forearm was performed with 0.1 ml. of 1:10 dilution of streptomycin. Twenty minutes later the tests were read and no reactions were noted.

Prior to the administration of the drug the patients were instructed to empty their bladders. A specimen of the urine was taken for urinalysis, the remainder being discarded. Thereafter, for the duration of the study, a record was kept of the intake and output of fluids in each patient.

A dose of 75,000 units of streptomycin in 5 ml. of solution was then injected intramuscularly. The time periods indicated in all the tables of this study denote the time elapsed following the first injection. The hour when the first injection was made is considered as the zero hour in the study. One hour later a blood specimen was taken for a determination of the concentration of streptomycin. The subjects were instructed to empty their bladders, the volume of urine was measured and recorded, and a specimen of the urine was taken for streptomycin assay. Similar specimens were taken and measurements made at the end of the second and third hours after the first injection. At this latter time, the patients received another 75,000 units of streptomycin intramuscularly, blood and urine specimens being collected before the injections were given. Thereafter, during this phase of the study, each patient received 75,000 units of streptomycin intramuscularly every 3 hours until a total of 600,000 units had been given in 8 injections.

The concentration of streptomycin in the blood and urine specimens are indicated in Tables I to IV. When the time of injection coincided with the time of the taking of the specimen, samples were obtained before the injections were given.

Twenty-four hours after the onset of the study, the dose of streptomycin was increased to 150,000 units in 10 ml. of solution intramuscularly every 3 hours. At this dosage level a total of 1,950,000 units of streptomycin were given in 13 injections from the twenty-fifth to the sixtieth hour of the study.

Beginning at the sixty-third hour, the dosage was reduced to the original level of 75,000 units in 5 ml. intra-

[1] The streptomycin used in this study was supplied by Merck and Co., Inc., and consisted of lots numbered 4R6040 and 4R6223.

TABLE I

Blood and urine concentration and excretion of streptomycin in relation to dosage by time periods
Subject—Nadherny

Time period	Urine output	Dosage	Blood concentration	Urine concentration	Excretion
hour †	*ml.*	*units per 3 hours*	*units per ml.*		*units*
Control			1.0 to 2.0		
1	375		1.0 to 2.0	40.0	15,000
2	100	75,000 intramuscularly for 8 doses	1.0 to 2.0	80.0	8,000
3	100		1.0 to 2.0	80.0	8,000
12	1,125		1.0 to 2.5	80.0	90,000
24	1,890		1.0 to 2.0	140.0	264,000
25			8.0		
26	200		13.0	160.0	32,000
27	450		6.0	140.0	63,000
36	800		13.0	400.0	320,000
37	200	150,000 intramuscularly for 13 doses		400.0	80,000*
38 } 39b	250			200.0	50,000*
39	150		18.0		
39b	600			240.0	144,000
48	1,790		10.0	180.0	322,000
60	1,375		8.0	270.0	371,000
63					
66		75,000 intramuscularly for 2 doses			
69					
72	3,975		5.0	70.0	278,250
84	1,410	None	1.0 to 2.5	40.0	56,400
93	600		1.0 to 2.5	20.0	12,000
94	600		1.0 to 2.5	2.5	1,500
95	800		1.0 to 2.5	0	0
96	700		1.0 to 2.5	2.5	1,750
97	500	31,250 orally** for 8 doses	1.0 to 2.5	2.5	1,250
109	1,750		1.0 to 2.5	2.5	4,375
117	1,340		1.0 to 2.5	2.5	3,350
120	800	None	1.0 to 2.5	0	0
132	2,150		1.25	2.5	5,375

* These 2 excretion values are not included in the total excretion because sample 39b includes the total excretion during hours 37 to 39 (881,200 units).
** Blood levels following oral administration reported on a basis of estimated unitage.
† Hour at which blood was taken.

muscularly for 2 doses. Intramuscular administration was then discontinued. These latter changes in dosage were made necessary by the toxic manifestations of the particular lot of drug studied.

From the sixty-ninth through the ninety-third hour, no further drug was administered but specimens of blood and urine were collected as indicated in Tables I to IV.

Beginning at the ninety-fourth hour and ending at the one hundred seventeenth hour, 31,250 units per dose of streptomycin were administered orally in capsules for 8 doses.

From the one hundred twentieth to the one hundred thirty-second hour, no further drug was administered but specimens were again collected as indicated in Tables I to IV.

Each day during the course of the study the following measurements were made on each patient: fluid intake and urinary output, urinalysis, complete blood count, blood urea nitrogen, erythrocyte sedimentation rate, blood pressure, and electrocardiogram. Temperature, pulse, and respiration were recorded every 4 hours throughout the day and night. An icteric index and a cephalin flocculation test were repeated at the end of the study.

Procedure for the assay of streptomycin in blood and urine [2]

The concentrations of streptomycin in the blood and urine were determined by a modification of

[2] The assay method used in this study was devised by one co-author (R. B. S.) in cooperation with Dr. H. J. Robinson. This method making use of *B. subtilis* as the test organism should not be confused with the more recently developed assay employing *Staphylococcus aureus* SM. (15), the latter method being more accurate than the present method which is not precise enough for levels below 5 units per ml. All levels below 5 units per ml. in this paper are estimates and are not to be considered as definite levels.

TABLE II

Blood and urine concentration and excretion of streptomycin in relation to dosage by time periods
Subject—Russo

Time period	Urine output	Dosage	Blood concentration	Urine concentration	Excretion
hour †	*ml.*	*units per 3 hrs.*	*units per ml.*		*units*
Control			1.0 to 2.0		
1	350		1.0 to 2.0	20.0	7,000
2	650	75,000 intramuscularly for	1,0 to 2.0	20.0	13,000
3	300	8 doses	1.0 to 2.0	40.0	12,000
12	675		2.5 to 5.0	100.0	67,500
24	2,765		6.0	100.0	276,500
25			18.0		
26	725		13.0	60.0	43,500
27	450		8.0	80.0	36,000
36	550		20.0	270.0	148,500
37		150,000 intramuscularly for			
38 } 39b	525	13 doses		240.0	126,000*
39	400		20.0		
39b	925			150.0	138,750
48	2,670		20.0	180.0	480,600
60	1,725		20.0	240.0	414,000
63		75,000 intramuscularly for			
66		2 doses			
69					
72	3,475	None	15.0	80.0	278,000
84	3,350		5.0	20.0	67,000
93	2,580		1.25	5.0	12,900
94	600		1.0 to 2.5	5.0	3,000
95	650		1.0 to 2.5	3.0	1,950
96	700	31,250 orally** for 8 doses	1.0 to 2.5	5.0	3,500
97	500		1.0 to 2.5	3.0	1,500
109	2,600		1.0 to 2.5	3.0	7,800
117	2,190		1.0 to 2.5	3.0	6,570
120	1,250	None	<1.25	3.0	3,750
132	1,220		<1.25	8.0	9,760

* This excretion value is not included in the total excretion because sample 39b includes the total excretion during hours 37 to 39 (138,750 units).

** Blood levels following oral administration reported on a basis of estimated unitage.

† Hour at which blood was taken.

the Foster-Woodruff assay method (14) for streptothricin. In order to increase the sensitivity of the method, all blood samples were hemolyzed by the addition of weighed amounts (0.5 to 1.0 mgm.) of saponin. This prevented the red cells in the blood samples from settling at the base of the penicylinders, thereby facilitating diffusion of the drug through the agar.

The concentration of streptomycin in blood was determined from a standard curve of reference for each blood assay. Dilutions of the drug standard (5, 10, 20, 40, 60, 80, 100 units per ml.) were made in normal hemolyzed blood, with the latter as diluent. The diameters of the resulting zones of cleared area were plotted as ordinates against the concentrations of streptomycin as abcissae.

Test bloods were diluted when necessary with normal hemolyzed blood to contain approximately 20 to 60 units per ml., otherwise the sample was assayed undiluted. Dilutions of the test sample and each standard level were run in duplicate. The concentration of streptomycin in a test sample was obtained by determining from the standard curve the drug concentration corresponding to the diameter of the zone of inhibition and correcting for the dilution.

Distilled water replaced whole hemolyzed blood as the diluent in the assay of the urine specimens.

In the preparation of agar plates for the assay, 0.1 ml. of a standardized *B. subtilis* [3] inoculum was added to each 100 ml. of molten (45 to 50° C.)

[3] Supplied by Microbiological Laboratories, Merck & Co., Inc.

F.D.A. agar. By means of a calibrated wide mouth pipette, 13 ml. of the seeded agar was delivered into each petri dish. After cooling and solidification of the agar, beveled glass penicylinders were warmed in a Bunsen flame and placed upon the agar surface resulting in an effective seal between the glass cylinder and the agar. The cylinders were then filled with the test samples. For the assay of blood specimens both the standard and the test samples were placed in the icebox overnight to insure complete diffusion of the drug through the agar plate but this was not necessary in the case of urine specimens. The plates were then incubated at 30° C. for 16 to 18 hours. The diameters of the cleared areas were then recorded in millimeters.

Absorption and excretion of streptomycin

Individual observations at various time periods in urine output, blood concentration, urine concentration and excretion of streptomycin in the 4 subjects studied are detailed in Tables I to IV. In these tables it will be noted that the concentration of streptomycin in the blood resulting from a dose of 75,000 units intramuscularly every 3 hours are very low and are at the same level as the control blood specimens. They are also in approximately the same range obtainable as a result of oral administration of 31,250 units every 3 hours. These levels are so low that they cannot accurately be determined by the method used, but it is obvious that they are below the expected range of therapeutic effectiveness of the drug against most of

TABLE III

Blood and urine concentration and excretion of streptomycin in relation to dosage by time periods
Subject—Schwaid

Time period	Urine output	Dosage	Blood concentration	Urine concentration	Excretion
hour †	*ml.*	*units per 3 hrs.*	*units per ml.*		*units*
Control			1.0 to 2.0		
1	500		2.5	20.0	10,000
2	350	75,000 intramuscularly for	1.0 to 2.0	70.0	24,500
3	400	8 doses	1.0 to 2.0	80.0	32,000
12	1,325		2.5 to 5.0	100.0	132,500
24	2,540		2.5	100.0	254,000
25			18.0		
26	150		20.0	140.0	21,000
27	175		18.0	100.0	17,500
36	640		13.0	320.0	204,000
37		150,000 intramuscularly for			
38 } 39b	125	13 doses		320.0	40,000*
39	200		18.0		
39b	325			200.0	65,000
48	1,615		8.0	200.0	323,000
60	450		10.0	400.0	180,000
63		75,000 intramuscularly for			
66		2 doses			
69					
72	1,075	None	8.0	60.0	64,500
84	1,825		5.0	90.0	164,250
93	1,400		2.5	15.0	21,000
94	700		1.0 to 2.5	8.0	5,600
95	300		1.0 to 2.5	20.0	6,000
96	200		1.0 to 2.5	10.0	2,000
97	200	31,250 orally** for 8 doses	1.0 to 2.5	10.0	2,000
109	1,750		2.5	5.0	8,750
117	1,490		2.5 to 5.0	5.0	7,450
120	250	None	1.25 to 2.5	8.0	2,000
132	740		<1.25	15.0	11,100

* This excretion value is not included in the total excretion because sample 39b includes the total excretion during hours 37 to 39 (631,000 units).

** Blood levels following oral administration reported on a basis of estimated unitage.

† Hour at which blood was taken.

TABLE IV

Blood and urine concentration and excretion of streptomycin in relation to dosage by time periods
Subject—Weiss

Time period	Urine output	Dosage	Blood concentration	Urine concentration	Excretion
hour †	*ml.*	*units per 3 hrs.*	*units per ml.*		*units*
Control			1.0 to 2.0		
1	325		1.0 to 2.0	20.0	6,500
2	75	75,000 intramuscularly for	1.0 to 2.0	150.0	11,250
3	200	8 doses	1.0 to 2.0	70.0	14,000
12	660		1.0 to 2.5	100.0	66,000
24	2,195		5.0	80.0	175,600
25			5.0		
26	300		13.0	40.0	12,000
27	400		10.0	80.0	32,000
36	500		8.0	280.0	140,000
37	50	150,000 intramuscularly for		400.0	20,000*
38–39b	225	13 doses		120.0	27,000*
39	350		13.0		
39b	625			120.0	75,000
48	2,015		10.0	200.0	403,000
60	355		6.0	200.0	71,000
63		75,000 intramuscularly for			
66		2 doses			
69					
72	2,695	None	5.0	70.0	188,650
84	2,125		1.25	20.0	42,500
93	1,500		2.5	10.0	15,000
94	700		1.25	0.0	0
95	400		1.25	2.5	1,000
96	400		1.0 to 2.5	2.5	1,000
97	350	31,250 orally** for 8 doses	1.0 to 2.5	2.5	875
109	1,250		1.0 to 2.5	2.5	3,125
117	1,660		1.0 to 2.5	0.0	0
120	650	None	1.0 to 2.5	0.0	0
132	490		<1.25	2.5	1,225

* These 2 excretion values are not included in the total excretion because sample 39b includes the total excretion during hours 37 to 39 (75,000 units).
** Blood levels following oral administration reported on the basis of estimated unitage.
† Hour at which blood was taken.

the microorganisms which have thus far been tested *in vitro* (3). However, the number of units excreted in the interval during intramuscular administration of 75,000 units every 3 hours is obviously much greater than the amount excreted as a result of the oral administration. This would indicate that very small amounts of the drug are absorbed when administered orally and that when somewhat larger amounts are absorbed, as in the intramuscular dosage of 75,000 units every 3 hours, the drug is excreted in the urine so rapidly that no significant blood level is attained.

In the second phase of the experiment, after increasing the dose to 150,000 units intramuscularly every 3 hours, the concentrations of the drug in the blood rose sharply into the range of therapeutic effectiveness and were maintained at that level despite excessive intake and output of fluid. Therefore, such levels can reasonably be expected to be attained with this dosage of the drug.

It is further evident from the study of Tables I to IV that even though the dosage of the drug was halved at the sixty-third hour and discontinued at the sixty-sixth hour, a measurable amount of the drug was still present in the blood until the seventy-second hour, and that excretion in the urine continued through the ninety-third hour.

The data in Table V are summarized in protracted time periods. The percentage excretion of the drug is relatively constant during the first 2 periods regardless of the increase in dosage dur-

ing the second period. However, during the third period in 2 of the 4 patients (S and W), when the urinary output dropped because of the toxic manifestations of the drug, there was a decrease in the output of the drug.

During the fourth period, following discontinuation of the drug administration at which time the output of urine increased in 3 of the 4 patients (R, S, and W), some of the retained drug was excreted. The small amount of drug absorbed when administered by mouth is reemphasized in Table V.

In Tables VI to IX, pertinent laboratory observations are summarized. This lot of drug produced a leukocytosis with an increase in polymorphonuclear leukocytes, an increase in the sedimentation rate and an increase in the formed elements in the urine. There was a concomitant decrease in the urinary output in 2 patients (S and W). Examination of the urine approxi-

TABLE V

Dosage, excretion, and cumulative excretion of streptomycin by time periods

Time periods	Streptomycin Dosage *	Fluid Intake	Urine output	Streptomycin excretion		
				Amount in each period	Percentage in each period	Cumulative percentage
			Subject—*N*			
hours	*units*	*ml.*	*ml.*	*units*		
	I.M.					
0 to 24	600,000	7,375	3,590	385,600	64.3	64.3
25 to 48	1,200,000	6,640	4,140	881,200	73.4	70.4
49 to 72	900,000	7,840	5,350	649,500	72.1	71.0
73 to 93	000,000	3,665	2,010	68,400		73.5
	P.O.					
94 to 117	250,000	7,160	5,690	12,225	4.9	67.7
118 to 132	000,000	2,000	2,950	5,375	2.2	67.9
			Subject—*R*			
hours	*units*	*ml.*	*ml.*	*units*		
	I.M.					
0 to 24	600,000	8,335	4,740	376,000	62.7	62.7
25 to 48	1,200,000	8,920	5,320	847,350	70.6	68.0
49 to 72	900,000	9,580	5,200	692,000	76.8	70.9
73 to 93	000,000	3,575	5,930	79,900		73.9
	P.O.					
94 to 117	250,000	7,855	7,240	24,320	9.7	68.5
118 to 132	000,000	2,500	2,470	13,510	5.4	68.8
			Subject—*S*			
hours	*units*	*ml.*	*ml.*	*units*		
	I.M.					
0 to 24	600,000	9,195	5,115	453,000	75.5	75.5
25 to 48	1,200,000	4,920	3,055	631,300	52.6	60.2
49 to 72	900,000	7,250	1,525	244,500	27.1	49.2
73 to 93	000,000	3,015	3,225	185,250		56.0
	P.O.					
94 to 117	250,000	3,215	4,640	31,800	12.7	52.4
118 to 132	000,000	1,000	990	13,100	5.3	52.9
			Subject—*W*			
hours	*units*	*ml.*	*ml.*	*units*		
	I.M.					
0 to 24	600,000	5,320	3,455	273,350	45.5	45.5
25 to 48	1,200,000	9,220	3,940	662,000	55.2	51.9
49 to 72	900,000	8,060	3,050	259,650	28.8	44.3
73 to 93	000,000	4,015	3,625	57,500		46.4
	P.O.					
94 to 117	250,000	4,875	4,760	6,000	2.4	42.6
118 to 132	000,000	2,000	1,140	1,225	0.5	42.6

* A total of 2,950,000 units were administered to each subject, the first 2,700,000 intramuscularly and the last 250,000 by mouth.

TABLE VI

Pertinent laboratory observations
Subject—Nadherny

	Blood counts								Urinalyses										Erythrocyte sedimentation rate†	Blood urea nitrogen	Cephalin flocculation	Icteric index	Blood pressure
	Hgb.	R.B.C.	W.B.C.	P	L	M	E	B	Sp. Gr.	Reaction	Albumin	Glucose	Bile	R.B.C.		W.B.C.		Casts††					
														C*	N.C.**	C*	N.C.**	C*	N.C.**				
hour																							
0	14.0	5.14	11,100	50	39	6	4	1	1.022	Acid	0	0	0	0	0	0	0	0	0	10	12	Negative	150/88
12	14.5		9,100	68	28	0	4	0	1.006	Acid	+	0		0	0	Rare	0	0	0	5	13		120/70
39	14.5		8,900	68	24	0	8	0	1.008	Acid	+	0	0	0	0	Rare	Rare	0	0	7	11		110/70
48			13,900	83	13	1	3	0	1.008		0	0	0	0	0	1 to 2	5 to 10	0	0		11		
60	15.5		11,200	75	23	0	2	0	1.008	Acid	+	0	0	0	0	Rare	Rare	0	0	11	13		120/80
84			9,650	74	16	6	4	0	1.010	Acid	0	0		0	0	Rare	Rare	0	0	18	16		130/80
120	13.5		8,600	80	16	0	4	0	1.008	Acid	0	0	0	Occasional	0	Rare	0	0	0	33	14	Negative	8	144/90
132									1.028	Acid	+	0	0	2 clumps	0 to 3	0	0	0	0	40			
231	13.0								1.016	Acid	+	0		0	0	Occasional	Occasional	0	0				125/80

* Centrifuged.
** Not centrifuged.
† Westegren method.
†† G = granular, H = hyaline, W = white blood cell, and R = red blood cell cast.

TABLE VII

Pertinent laboratory observations
Subject—Russo

	Blood counts								Urinalyses										Erythrocyte sedimentation rate†	Blood urea nitrogen	Cephalin flocculation	Icteric index	Blood pressure
	Hgb.	R.B.C.	W.B.C.	P	L	M	E	B	Sp. Gr.	Reaction	Albumin	Glucose	Bile	R.B.C.		W.B.C.		Casts††					
														C*	N.C.**	C*	N.C.**	C*	N.C.**					
hour																								
0	13.0	4.46	7,250	62	36	2	0	0	1.024	Acid	+	0	0	0	0	0	0	0	0	10	9	Negative	5	150/90
12	15.0		8,550	84	15	1	0	0	1.008	Acid	0	0		0	0	Rare	Rare	0	0	12				
24			14,320	82	15	2	0	1	1.008	Acid	0		0		0		Rare		0		11			130/80
27									1.005	Acid	0	0	0		0		0		0					
39	12.5		9,250	82	15	1	2	0	1.005	Acid	++	0	0		7		0			28	15			
48			11,300	77	19	4	0	0	1.010		++	0	0	0	0	Many clumps	0 to 2 Rare clumps	Moderate G, W and R	Rare G, W and R		13			120/80
60	13.1		9,400	78	21	0	0	1	1.002	Acid	++	0	0		Occasional		Occasional		Occasional G, H and R	41	14			122/80
84			6,950	62	30	6	1	1	1.004	Acid	++	0		1 to 2	1 to 2	Numerous	Numerous	Numerous W, occasional G, rare R	Numerous W, rare G	52	15			115/85
94									1.002	Acid	++	0	0	Occasional	Rare	0	0	Rare H, G and R	Rare H and G		21			
120	13.0		5,750	78	18	2	2	0	1.006	Acid	++	0	0	2 to 4 clumps	0 to 2	Occasional	0	Occasional H and G	Occasional H and G	56	16	Negative	8	140/90
132									1.012	Acid	+++	0	0	Masses	5 to 12	0	0		Rare H, G, R and W	49				
231	12.3								1.002	Neutral	++	0		0	0	Rare	0 to 1	Rare G and H	Rare G					155/90

* Centrifuged.
** Not centrifuged.
† Westegren method.
†† G = granular, H = hyaline, W = white blood cell, and R = red blood cell cast.

TABLE VIII

Pertinent laboratory observations
Subject—Schwaid

	Blood counts								Urinalyses										Erythrocyte sedimentation rate†	Blood urea nitrogen	Cephalin flocculation	Icteric index	Blood pressure
	Hgb.	R.B.C.	W.B.C.	P	L	M	E	B	Sp. Gr.	Reaction	Albumin	Glucose	Bile	R.B.C.		W.B.C.		Casts††					
														C*	N.C.**	C*	N.C.**	C*	N.C.**				
hour 0	14.0	5.40	6,750	76	20	4	0	0	1.023	Acid	+	0	0	0	0	0	0	0	0	9	16	Negative		170/110
12	13.8		6,500	78	21	1	0	0	1.008	Acid	+	0		0	0	Rare	0	0	0	8	13			160/110
39	14.0		8,200	84	16	0	0	0	1.008	Acid	+	0	0	0	0	Rare	Rare	0	0	13	10			140/110
48			12,000	85	10	5	0	0	1.005		0	0	0	0	0	0	0	Rare H	0					112/80
60	17.0		9,500	76	21	3	0	0	1.022	Acid	++	0	0	5 to 6	Rare	0	Occasional clump	3 to 4 H and G	1 to 2 H and G	15	15			124/84
84			8,900	74	20	6	0	0	1.002	Acid	+	0		Rare	0	1 to 3	Rare	0	0	26	16			120/80
117	13.0		6,350	76	18	0	6	0	1.008	Acid	0	0	0	Rare	0	Rare	0	0	0	22	14	Negative	9	120/76
132									1.020	Acid	+	0	0	0 to 1 clump	Rare	0	0	Occasional G and H	0	36	17			
231	14.0								1.020	Neutral	++	0		Rare	Rare	Occasional	Occasional	0	0					140/90

* Centrifuged.
** Not centrifuged.
† Westegren method.
†† G = granular, H = hyaline, W = white blood cell, and R = red blood cell cast.

TABLE IX

Pertinent laboratory observations
Subject—Weiss

	Blood counts								Urinalyses											Erythrocyte sedimentation rate†	Blood urea nitrogen	Cephalin flocculation	Icteric index	Blood pressure
	Hgb.	R.B.C.	W.B.C.	P	L	M	E	B	Sp. Gr.	Reaction	Albumin	Glucose	Bile	R.B.C.		W.B.C.		Casts††						
														C*	N.C.**	C*	N.C.**	C*	N.C.**					
hour																								
0	14.5	5.30	10,520	61	33	6	0	0	1.023	Acid	+	0	0	0	0	0	0	0	0	7	13	Negative	4	130/90
12	14.5		8,330	88	12	0	0	0	1.018	Acid	++	0		0	0	Rare	Occasional	Rare G	0	5	10			120/60
39	15.0		9,100	72	22	2	4	0	1.005	Acid	+	0	0	0	0	Occasional	Occasional	G and H	G and H	13	11			118/68
48			13,900	76	15	8	1	0	1.002		0	0	0	0	0	1 to 3	Rare	0	0		7			
60	17.5		12,400	68	29	1	2	0	1.002	Acid	++	+	0	0	0	0	Rare	Occasional H and G	0	23	16			128/80
84			9,800	70	25	4	0	1	1.004	Acid	+	0		0	0	Rare	Rare	0	0	31	12			120/80
120	12.2		6,500	70	28	1	1	0		Acid	+	+++	0	Rare	0	0	Occasional	Rare H	0	15	13	Negative	12	120/70
132									1.012	Acid	+	0	0	0	0	Occasional	Rare	0	0	31				
231									1.012	Acid	+	0	0	0	0	Occasional	Rare	0	0					118/80

* Centrifuged.
** Not centrifuged.
† Westegren method.
†† G = granular, H = hyaline, W = white blood cell, and R = red blood cell cast.

mately 4 days following the completion of the experiment at the two hundred thirty-first hour showed a decrease in the abnormal findings in the urine.

The patients also developed fever and signs of inflammation at the sites of injection. From more recent experience in the use of this drug (16) the toxic manifestations demonstrated by the 2 lots of drugs studied would be considered atypical and have not resulted from therapy with subsequent lots of streptomycin. The only change noted in the cardiovascular system was a depression in the systolic and diastolic blood pressure which became manifest very early in the course of drug administration as indicated by the blood pressure measurements at the twelfth hour in Tables VI to VIII. The daily electrocardiograms showed no significant changes.

The data in 2 recent publications (17, 18), utilizing the same method of assay described in this paper, could not be compared with these results since the minimum period for which data were presented in those studies was 24 hours.

Typhoid carrier study

The stool cultures taken prior to the administration of the drug were all strongly positive for *B. typhosus*. The typhoid bacilli isolated from patient R proved to be type E, and that from patient W, type A. The typhoid bacilli isolated from the other 2 patients did not type. The sensitivity of the typhoid bacilli to streptomycin ranged between 10 and 20 units per ml. (S = 10 units per ml.; N, R, and W = 20 units per ml.).

There were no significant changes in the number of typhoid bacilli in the stools of any of the patients during the intramuscular administration of the drug. Stool specimens from 2 of 3 patients (from patient S and W but not from patient R), obtained at the end of the 24-hour period of oral administration of 31,250 units of the drug every 3 hours, were negative for typhoid bacilli but were positive again 12 hours later.

The urine cultures were negative prior to therapy and remained so.

SUMMARY AND CONCLUSIONS

1. Absorption and excretion of streptomycin following intramuscular and oral administration were studied in 4 human typhoid carriers. Streptomycin was administered every 3 hours in a dosage of 75,000 and 150,000 units intramuscularly and 31,250 units orally.

2. Following intramuscular administration of streptomycin approximately 60 to 70 per cent of the drug was excreted in the urine during a 24-hour period. Appreciable amounts of the drug were not absorbed from the gastrointestinal tract following repeated administration of capsules containing 31,250 units.

3. Blood concentrations of streptomycin following administration of 75,000 units intramuscularly every 3 hours ranged from 0 to 6 units per ml. and when the dose was increased to 150,000 units every 3 hours, the level rose to 5 to 20 units per ml.

4. Certain toxic manifestations unique for these particular lots of drug were noted.

5. At a dosage level of 75,000 or 150,000 units intramuscularly every 3 hours, no significant bacteriostatic effect on the typhoid bacilli in the stool was obtained. Following oral administration of 31,250 units every 3 hours, a definite transitory bacteriostatic effect on the typhoid bacilli in the stool was obtained in 2 of 3 patients.

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