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STUDIES ON THE CONCENTRATION OF STREPTOMYCIN IN THE TREATMENT OF TUBERCULOSIS OF THE JOINTS

By

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In streptomycin treatment of tuberculosis of the joints the dosage schedule established for tuberculosis of other organs has generally been applied. This dosage is based on detailed studies of the absorption and excretion of streptomycin in most of the body fluids and cavities. However, these original works (3, 5) which were published soon after the discovery of streptomycin, contain no data concerning absorption in cases of bone and joint tuberculosis. Some investigations on this subject have subsequently appeared in the literature, but the observations are so few in number that no clear and uniform picture of the absorption can be obtained. *Jones* (4) examined the joint exudate in one case of tuberculous synovitis of the knee treated by local injections. He found that after repeated injections of a total amount of 5½ g, streptomycin was still present in the joint three weeks after the last injection, which indicated a cumulative effect. *Ahern* and *Arden* (1) determined the streptomycin content in the blood after local administration in four cases, but did not examine the joint exudate. *Streeten* (6), without presenting any further details, states that 24 hours after an intraarticular injection the concentration of streptomycin in the joint exudate is a quarter to half of the original content at the time of injection, and that with daily injections the concentration is not likely to fall below 500 μg per ml. So far as I can find, these are the only published data concerning the absorption of streptomycin in cases of tuberculosis of the joints.

To find out the suitable dosage scheme for streptomycin therapy in bone and joint tuberculosis, the absorption was examined systematically in a series of cases of this kind. The results obtained after de-

termining the dihydrostreptomycin[1] concentration in cases of tuberculous osteitis with secondary abscesses have been published elsewhere (2). The present paper gives the results of such tests in cases of tuberculous synovitis.

No clear information concerning the desirable concentration of streptomycin *in vivo* is to be found in the literature. *Youmans* et al. (8), in experiments *in vitro,* observed that tubercle bacilli cultured from sputum were in most instances primarily sensitive; 90 per cent were inhibited by streptomycin in a concentration below 1.56 μg per ml. In three of the examined cases of tuberculous synovitis in the present material, in which the resistance was tested, complete inhibition occurred at a streptomycin concentration of 3.1 μg, 0.77 μg, and 0.38 μg per ml, respectively. Thus, the minimum effective concentration *in vivo* would appear to be 1–2 μg per ml.

Material and methods. Because of the difficulties in obtaining material for examination, only cases of markedly exudative synovitis of the knee-joint could be examined, nine cases in all. The streptomycin concentration was determined from joint exudate and blood serum, and in a few cases also from the urine. It was followed serially by repeated tests in order to obtain absorption curves. Sporadic tests were also made during the course of treatment to check the effectiveness of the dosage used. In the serially tested cases the needle was not removed during the period of examination. For the intraarticular administration the drug was dissolved in a buffer solution of pH 9.0, which is considered to give optimal effect.

Assay. The determinations of the streptomycin concentration were carried out at the State Bacteriological Laboratory, Stockholm, according to a method described by *Wallmark* (7), which is a modification of the cylinder-cup method devised by *Heetley.* Small capillary beads, so-called fish-spine insulators, are used in place of the usual glass cylinders. A suitable amount of a sensitive staphylococcus strain is spread on an agar plate, and beads filled with the sample and with a streptomycin solution of known concentration, respectively, are then placed on the agar surface. After incubation at 37°C. over-night the zones of inhibition are measured. By means of a standard curve the content of streptomycin in the sample is then estimated. This micro-biologic diffusion method appears to be very reliable. It is estimated that the standard error of the results obtained fall within a range of ±15 %.

RESULTS

General treatment. In three cases samples of joint exudate and blood were examined simultaneously by repeated tests after a single *intramuscular* injection of ½ g of streptomycin. The results are

[1] In the following streptomycin refers to dihydrostreptomycin.

TABLE 1

Concentration of Streptomycin in μg/ml following a Single Intramuscular Injection.

Case No.	Dose in g		Time in Hours after Injection													
			1	2	3	4	5	6	7	8	9	10	11	12	15	18
1	0.5	Exudate	1.3	2.3	2.9	2.5	3.5	3.6	3.4	3.4	3.2	1.2				
		Blood	11.0		7.1		4.9		1.5		1.5					
2	0.5	Exudate	2.2	3.2	4.9	3.7	3.6	3.9		4.2		2.0		1.1		
		Blood	32.0		8.5		5.6		3.0		0.5		0			
3	0.5	Exudate	0.9	3.5	5.0	5.8	3.1	6.3	7.1	5.4	3.1	2.9	2.8			
		Blood	6.3		8.0		4.9		2.4		1.2		<0.5			
4	1.0	Exudate	3.7	13.2	6.9			5.6			5.2			3.0	1.0	0
		Blood	19.5		17.8			7.7			3.0			1.3		0

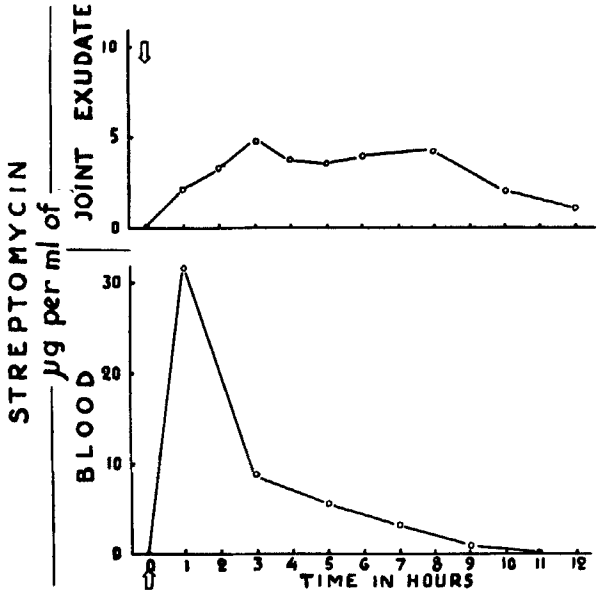

Fig. 1.

Streptomycin in blood and joint exudate following a single *intramuscular* injection of ½ g. Case 2. In all the charts *intramuscular* injection is indicated by a white arrow , and *intraarticular* administration by a solid black arrow

shown in table 1 and figs. 1 and 2. It will be seen that a slowly rising curve is produced, with a maximum concentration of about 5 µg per ml of joint exudate three to eight hours after injection, followed by a slow decline. After 10–11 hours the effective level is still maintained. The blood curve is of the usual configuration. Fig. 2 shows a mean curve for the three examined cases and the curve representing the concentration after the injection of 1 g intramuscularly. In the latter case there is a more marked initial rise, but six hours after injection the level is not significantly higher than it is after the smaller dose.

TABLE 2

Concentration of Streptomycin in µg/ml following a Single Intramuscular Injection.

Case No.	Dose in g		Time in Hours after Injection							
			12	13	14	15	16	17	18	21
1	1.0	Exudate	0.8			<0.5			<0.5	
		Blood	1.8			1.0				
5	1.0	Exudate	2.4	3.2	2.8	1.7	<0.5	<0.5		
6	1.0	Exudate	6.2			4.7			3.2	2.0
		Blood	8.5			3.5			1.6	

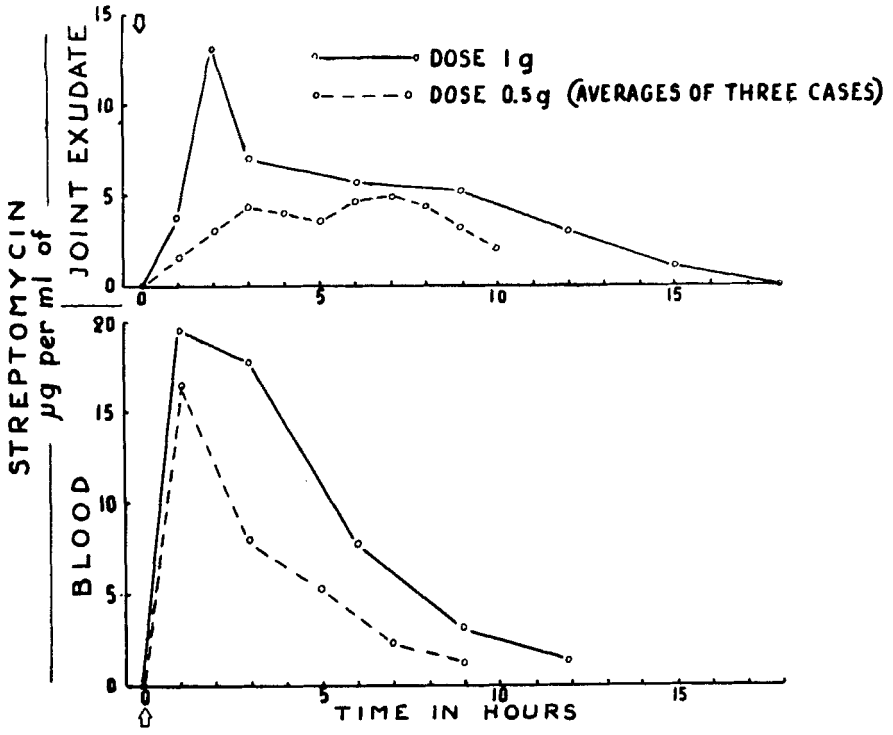

Fig. 2.
Streptomycin in blood and joint exudate following a single *intramuscular* injection. Cases 1, 2, 3, 4.

From a clinical point of view it is of the greatest interest to find out for how long streptomycin remains in the joint in a content sufficiently high to produce bacteriostatic effect. To clarify this question, further serial tests were made in three cases, starting 12 hours after the intramuscular injection, the dose being 1 g, which subsequently

TABLE 3
Concentration of Streptomycin in μg/ml following a Single Intraarticular Injection.

Case No.	Dose in g		Time in Hours after Injection							
			1	2	3	4	5	6	7	8
1	1.0	Exudate	2300		2240	720		710		
		Blood	6.2		4.4		3.9		4.0	
7	1.0	Exudate	6600	9800	4700	3000	1000	280		145
		Blood	7.4	9.6	4.4	8.7	3.8	3.9		2.6
8	1.0	Exudate		690	630	490				
		Blood		20	11	8.9				

became the standard dose in the treatment. The results are given in table 2. It will be seen in tables 1 and 2 that the effective level is maintained for about 12 hours after the injection of ½ g, and for about 15 hours after the injection of 1 g intramuscularly (in one of the cases for 21 hours).

In two of the cases the serial tests were repeated after one week's continuous intramuscular administration in doses of ½ g twice daily. A similar curve was obtained (fig. 3). Thus, there is no evidence of a cumulative effect, at any rate not after one week's intramuscular therapy.

Local treatment. Three cases were examined after a single injection of 1 g of streptomycin *intraarticularly,* table 3 and figs. 4 and 5. As was expected, the concentration in the joint exudate was very high. It fell successively during the day, and was still very high at the last test. The blood streptomycin level was also relatively high after intra-articular administration alone, and remained high for several hours, as long as, or longer than that after an intramuscular injection. The curve for the blood resembles that for the exudate after intramuscular administration (cf. fig. 1), which indicates that the drug passes the synovial membrane at approximately the same rate in both directions, from the joint cavity and the general circulation, respectively.

The excretion of streptomycin in the urine was also studied in these three cases. The content of excreted streptomycin in the different portions of urine is seen in fig. 5. However, the amount of streptomycin excreted during the 24 hour period following the intraarticular injection varied considerably in the three cases, being 15 %, 28 %, and 70 %, respectively, of the administered dose, and therefore no conclusions can be drawn from these tests only. For the sake of comparison,

TABLE 4

Concentration of Streptomycin in μg/ml following a Single Intraarticular Injection.

Case No.	Dose in g		Time in Hours after Injection								
			24	25	26	27	28	29	30	33	36
1	1.0	Exudate ...	16.6			7.7					
		Blood	5.0			0.7			0.8		
4	1.0	Exudate ...	3.2			2.2			1.1	<0.5	
		Blood	2.0			0			0	0	
5	1.0	Exudate ...	3.5		3.8		1.9		<0.5		
6	1.0	Exudate ...	7.2			5.5			5.9	4.3	3.5
		Blood	2.2			1.7			1.7		

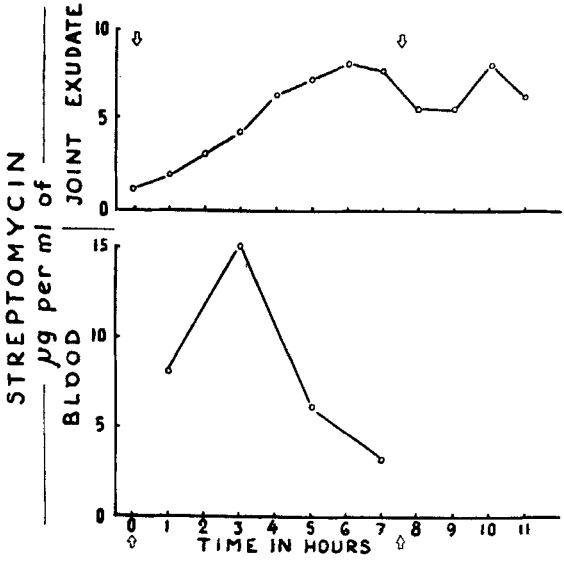

Fig. 3.

Streptomycin in blood and joint exudate during treatment with ½ g twice daily. The test was made after a seven day course. Case 3.

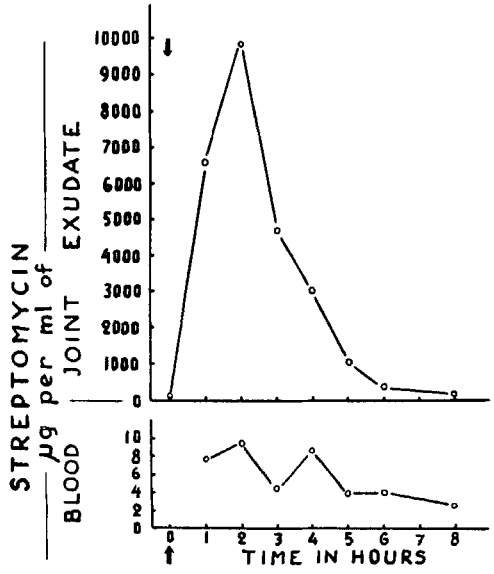

Fig. 4.

Streptomycin in blood and joint exudate following a single *intraarticular* injection of 1 g. Case 7.

TABLE 5

Concentration of Streptomycin (µg/ml) in Joint Exudate During Intraarticular Treatment.

Case No.	Intervals between Injections							
	24 hrs.		48 hrs.		72 hrs.		96 hrs.	
7	4.9	12.6	4.4	24.0				
	5.5	22.4						
	56.0	38.0						
8	14.1	4.0	0					
	19.5	10.5						
	4.7							
9					<0.5		0	0

it may be mentioned that in the literature 50–80 % is the amount quoted for the excretion during the 24 hour period following an intramuscular injection.

In applying local treatment it is also of interest to know how long streptomycin remains in the joint in effective concentration. Since the tests described above gave no information in this respect, further serial examinations were made, starting 24 hours after the local injection. The results, given in table 4, varied slightly; the effective level is apparently maintained for 30 hours, often longer.

At the beginning of this investigation *intraarticular therapy alone* was given in the cases of tuberculous synovitis. During the course of this treatment the drug was administered at varying intervals and the concentration was determined in samples collected immediately before the injections in order to find out the most suitable interval. The results are shown in table 5. When the injections were given at inter-

TABLE 6

Minimum Concentration of Streptomycin (µg/ml) in Joint Exudate During Combined General and Local Treatment.

Case No.	Intervals between local Injections					
	48 hrs.		72 hrs.		96 hrs.	
4	0.5	1.6	<0.5	1.7		
			1.0	2.0	1.4	0
5			6.2	<0.5	<0.5	0
			0	0	<0.5	
6	1.5	2.0	1.9	3.5	2.4	
	4.0		1.0			

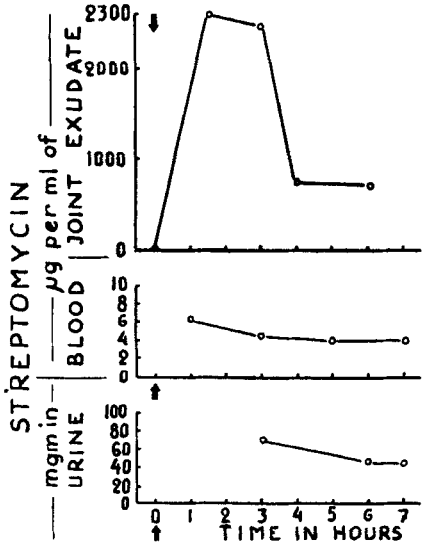

Fig. 5.

Streptomycin in blood, joint exudate and urine following a single *intraarticular* injection of 1 g. Case 1.

vals of three to four days no, or merely traces of, streptomycin remained in the joint exudate immediately before the next injection. With daily doses the effective level was maintained from one injection to the next. When the drug was given on alternate days, no streptomycin was recovered in the exudate in one case. In another there was a marked increase in the concentration during the course of treatment, which indicated a cumulative effect, observable only in this particular case, however.

Conclusions. In brief, the investigation has shown that in tuberculous synovitis streptomycin is excreted in the joint in effective concentration after *intramuscular* administration alone. The streptomycin level in the exudate remains sufficiently high to produce bacteriostatic effect for at least 12 hours after a dose of 1 g, as a rule for 15 hours, and occasionally longer. After administration of 1 g by the *intraarticular* route alone, the drug remains in the exudate for at least 30 hours, usually for about 48 hours.

As a result of these observations the following dosage schedule for streptomycin therapy in tuberculous synovitis has been worked out. A single daily dose of 1 g is given intramuscularly together with 1 g twice a week intraarticularly. The joint is also fixed in plaster of Paris. In some of the cases treated earlier the joint was not immobilized during treatment; others have also tried this. But since the result

was clinically unsatisfactory, we now use combined chemotherapy and immobilization. The treatment is given over a period of six weeks.

To keep a check on the streptomycin level under this regimen, further determinations of the concentration were made during treatment in three cases. The results are shown in table 6. The samples were collected immediately before administration, that is, 24 hours after the previous intramuscular injection. Thus, the figures represent minimum values for the streptomycin content during treatment. In most cases it is apparently sufficient to give local injections every third to fourth day. On a few occasions there was no detectable level of streptomycin, but as this lasted for a very short time, it is not likely to have influenced the therapeutic result. A cumulative effect was not obtained in these cases. It should be mentioned that the determinations were made both with and without immobilization of the joint, with no apparent difference in the absorption.

SUMMARY

Determinations of the concentration of streptomycin were carried out according to a microbiologic diffusion method in cases of tuberculous synovitis. The following results were obtained.

The synovial membrane does not constitute a barrier. The drug is absorbed at the same rate in both directions, from the general circulation and the joint cavity, respectively. Streptomycin is excreted in the joint in effectively high concentration after *intramuscular* administration alone, and the streptomycin level in the exudate remains sufficiently high to produce bacteriostatic effect for at least 12 hours after injection of 1 g, usually for 15 hours. After administration of 1 g by the *intraarticular* route alone the drug remains in the exudate for at least 30 hours, as a rule for 48 hours. With *combined general and local therapy* in doses of 1 g daily intramuscularly and 1 g intraarticularly twice a week the concentration of streptomycin in the joint exudate appears to be sufficiently high to control the tuberculous infection.

RESUME

Les déterminations de la concentration en streptomycine ont été pratiquées suivant un mode de diffusion microbiologique dans des cas de synovite tuberculeuse. Les résultats suivants ont été obtenus.

La membrane synoviale ne constitue pas un obstacle. Le médicament est absorbé au même taux dans les deux sens, de la circulation générale et de la cavité articulaire, respectivement. La streptomycine

est excrétée dans l'articulation à une concentration effectivement élevée après une injection *intramusculaire* seulement, et le taux de la streptomycine dans les excrétions reste suffisamment élevé pour produire un effet bactériostatique pendant au moins 12 heures après l'injection de 1 g, ordinairement pendant 15 heures. Si l'on administre 1 g par voie *intraarticulaire* seulement, le médicament se maintient dans les excrétions pendant au moins 30 heures, en règle générale pendant 48 heures. En appliquant une *thérapie générale et locale combinée* à doses journalières de 1 g par voie intramusculaire et de 1 g deux fois par semaine par voie intraarticulaire, la concentration de streptomycine dans les excrétions de l'articulation semble être suffisamment élevée pour mettre l'infection tuberculeuse sous contrôle.

ZUSAMMENFASSUNG

Konzentrationsbestimmungen von Streptomycin wurden nach einer mikrobiologischen Diffusionsmethode in Fällen von tuberkulöser Synovitis ausgeführt. Die folgenden Resultate wurden erhalten.

Die Synovialmembran stellt keine Schranke dar. Das Mittel wird nach beiden Richtungen hin im gleichen Ausmasse aufgesaugt, d.h. vom Kreislauf und von der Gelenkshöhle. Streptomycin wird nach intramuskulärer Injektion allein in wirkungsvoll hoher Konzentration in das Gelenk ausgeschieden und die Konzentration im Exudat bleibt auf einer Höhe, die genügend ist, um einen bakteriostatischen Effekt für zumindest 12 Stunden nach der Injektion von 1 g, gewöhnlich aber für 15 Stunden, zu erzeugen. Nach Verabreichung von 1 g in das Gelenk allein verbleibt das Mittel zumindest 30 Stunden im Exudat, meist jedoch 48 Stunden. Mit der kombinierten allgemeinen und örtlichen Behandlung in Dosen von 1 g täglich intramuskulär und 1 g intraartikulär zweimal wöchentlich scheint die Konzentration von Streptomycin im Gelenksexudat eine Höhe zu erreichen, die zur Beherrschung der tuberkulösen Infektion ausreichend ist.

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