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PENETRATION OF ANTITUBERCULAR DRUGS IN CLINICAL OSTEOARTICULAR TUBERCULAR LESIONS

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In 79 consecutive cases of skeletal tuberculosis the concentration of streptomycin and ethambutol was analysed. The material for analysis was obtained from the diseased joints of 14 patients and from cold abscesses from spinal or osseous lesions in 65 patients. The concentration of the drugs in the serum and in the tuberculous material was measured 3 hours after the systemic administration of the drugs in therapeutic doses. The concentration was expressed as μg per ml of the tuberculous material and the data were subjected to statistical analysis. Streptomycin and ethambutol penetrated freely into the tuberculous joints; their concentration in the cold abscesses, however, was half to one third of the concentration in the serum. There was a wide range of concentrations; however, in the tuberculous joints as well as in the cold abscesses the concentrations were much higher than those considered to have an inhibitory effect on mycobacterium tuberculosis in clinical material.

Key words: antitubercular drugs; osteoarticular tuberculosis; drug penetration; ethambutol; streptomycin

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It has long been presumed that antitubercular drugs do not reach osteoarticular tuberculous lesions in adequate concentrations, and universal radical excisional surgery has been practised and advocated by many workers to ensure penetration of the drug into skeletal tuberculous lesions. In recent times, however, a few clinical reports, especially from the developing countries, have been published, proving the efficacy of antitubercular drugs. The quality, rapidity, consistency and durability of healing in clinical material led many workers to infer that the drugs were indeed reaching the site of infection (Lindberg 1967, Friedman & Kapur 1973, Medical Research Council 1973, Tuli 1975). To resolve the controversy regarding the power of penetration of anti-tuberculous drugs an experimental study was reported in 1974 by the senior author proving the easy accessibility of the experimental osseous tuberculous lesions to streptomycin (Tuli et al. 1974). The present study was undertaken to determine the concentration of streptomycin and ethambutol in clinical osteoarticular tuberculous lesions.

MATERIAL AND METHODS

Consecutive unselected cases of osteoarticular tuberculosis who could provide an aspirable tuberculous material in the form of a tuberculous joint effusion or a cold abscess were included in this study. During preliminary work, a material of diseased osseous tissue, granulation tissue and sequestra, obtained from patients undergoing direct surgery for diagnostic or therapeutic purposes, was also collected. However, this was later excluded from the present report because of frequent mixing with blood, and a lack of control of the time interval for collection of the samples. Cases with doubtful diagnosis, and with gross secondary infection were also excluded. Thus for the final assessment material from 79 cases was available.

The age of the patients varied between 8 months and 60 years; there were 38 males and 41 females. The disease in all the patients was active and well established. Fourteen patients had tuberculosis of joints (Group I); 13 knee joints and one elbow. Group II consisted of 65 patients who provided material from an iliopsoas abscess in 34 cases and a cold abscess in other parts of the body in 31 cases. One of these patients provided 2 samples from cold abscesses in the arm and thigh. The majority of the patients showed varying degrees of tubercular cachexia, and haemoglobin concentration on an average was 10 g per cent.

Administration of drugs and aspiration of material

The patients were weighed and were administered streptomycin sulphate intramuscularly in doses of 25 mg per kg of body weight (not exceeding one g) well away from the site of proposed aspiration. Ethambutol hydrochloride 25 mg per kg of body weight was given by mouth on an empty stomach. The drugs were administered for 2 consecutive days and on the second day, 3 hours after the administration, blood and tuberculous material were aspirated under aseptic conditions. Special care was taken to avoid mixing of blood with the tuberculous aspirate.

Assay of the drugs

The broth dilution microbiological bioassay technique (Kolmar et al. 1969) was used for estimating the concentration of streptomycin in serum and the aspirate. For ethambutol, a chemical assay technique was employed (Allen & Baker 1968).

Reassessment

After the first investigation the patients were put on the standard triple drug therapy consisting of streptomycin INH, and ethambutol/PAS. Four patients from Group II provided the aspirable material for re-analysis, 3 to 5 months after the onset of their treatment.

RESULTS

Observations regarding concentration of drugs in the joint aspirate and serum in Group I are summarised in Table 1, and

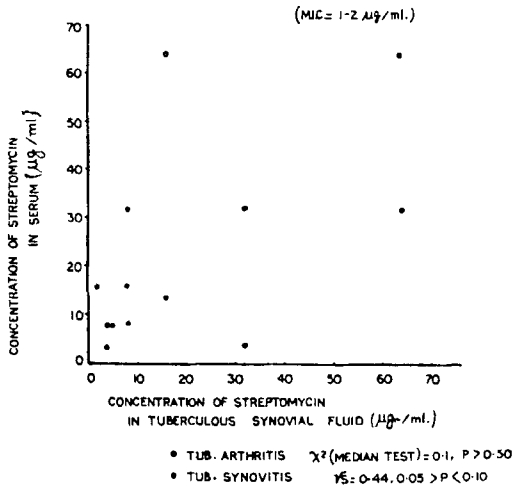

Figure 1. Correlation between the concentration of streptomycin in serum and in tuberculous synovial fluid (Group I).

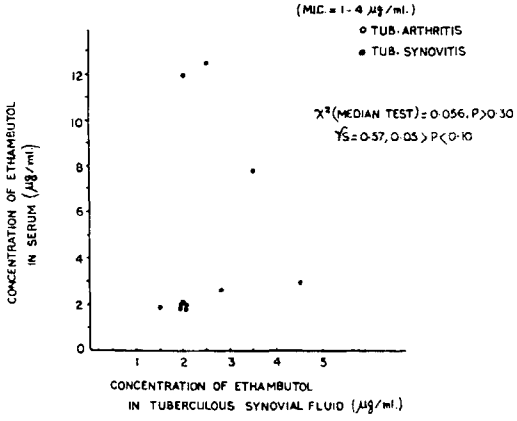

Figure 2. Correlation between the concentration of ethambutol in serum and in tuberculous synovial fluid (Group I).

Table 1. Concentration of streptomycin and ethambutol in serum and tuberculous joint aspirate (μg/ml).

Drug	Sample	No. of cases	No. estimated	Range of concentration	Average concentration	Median concentration
Streptomycin	Serum	14	13	3.5–64.0	23.34	16.0
	Joint aspirate	14	14	3.5–64.0	19.21	8.0
Ethambutol	Serum	14	11	1.9–12.5	4.51	2.0
	Joint aspirate	14	12	1.5–14.2	3.41	2.0

Table 2. Concentration of streptomycin and ethambutol in serum and cold abscess (μg/ml).

Drug	Sample	No. of cases	No. estimated	Range of concentration	Average concentration	Median concentration
Streptomycin	Serum	65	52	1.0–64.0	13.47	8.0
	Cold abscess	66	55	0.5–32.0	6.03	4.0
Ethambutol	Serum	65	53	3.0–16.0	10.17	12.0
	Cold abscess	66	50	1.3–10.5	3.21	2.5

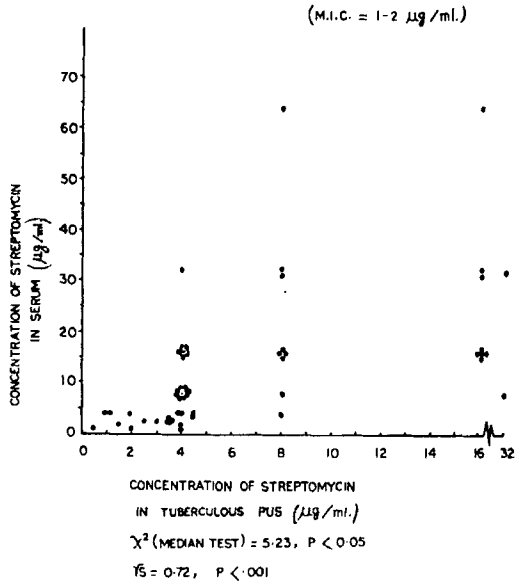

Figure 3. Correlation between the concentration of streptomycin in serum and in tuberculous cold abscess (Group II).

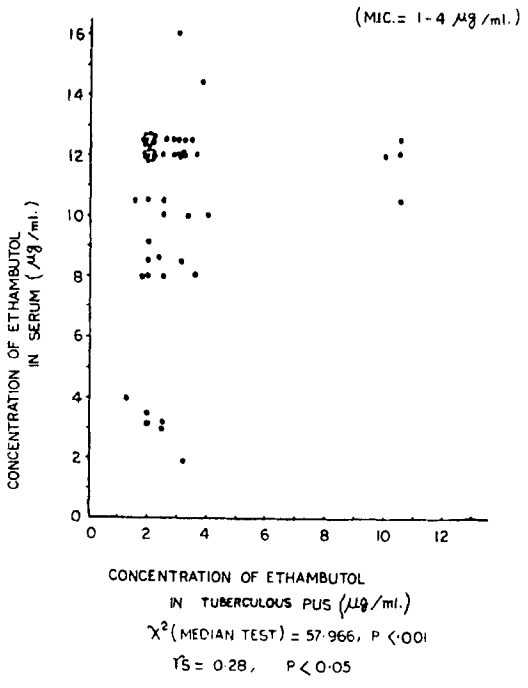

Figure 4. Correlation between the concentration of ethambutol in serum and in tuberculous cold abscess (Group II).

Figures 1 and 2. The corresponding observations in Group II (66 samples from 65 patients) are shown in Table 2, and Figures 3 and 4.

Concentration of streptomycin in serum

In Group I and Group II the range of concentration was 3.5–64.0 μg per ml. Statistically the range in both groups was almost equal, the average concentration, however, was 23.34 μg per ml in Group I and 13.47 μg per ml in Group II. This difference between the two groups, though statistically insignificant (median = 8, $x^2 = 2.41$, $P > 0.10$) may be explained on the basis of the relatively better general condition of the patients in Group I.

Concentration of streptomycin in joint aspirate

The concentration in the joint aspirate was observed to be almost equal to that of the serum (median = 16, $x^2 = 0.1$, $P > 0.50$) meaning that streptomycin flows freely from the serum into the joint without any functioning barrier.

Concentration of streptomycin in cold abscess

The range of concentration in 66 samples was 0.5–32.0 μg per ml, with an average of 6.03 μg per ml and median concentration of 4.0 μg per ml. It was observed that there was a significant difference between the serum and pus concentrations (median = 8, $x^2 = 5.23$, $P < 0.05$). Spearman's rank correlation coefficient (rs = 0.72, $P < 0.001$) suggested a strong correlation, i.e., with higher serum concentration there was a corresponding rise in the concentration in the abscess. In general the concentration in the cold abscess was one third of that in the serum.

Concentration of ethambutol in serum

The concentration in Group I ranged between 1.9–12.5 μg per ml with an average of 4.51 μg per ml. In Group II the range was 3.0–16.0 μg per ml and average 10.17 μg per ml. There was no statistically significant difference between the concentrations of Group I and Group II (medium = 12, $x^2 = 1.13$, $P > 0.20$).

Concentration of ethambutol in joint aspirate

The average concentration in tubercular joint aspirate was almost equal to the concentration in the serum (median = 2, $x^2 = 0.05$, $P > 0.30$). Like streptomycin ethambutol also appeared to penetrate freely into the tuberculous joints.

Concentration of ethambutol in cold abscess

The concentration of ethambutol in the cold abscess was almost one third of the concentration in the serum. The difference was statistically significant (median = 8, $x^2 = 57.96$, $P < 0.001$). Spearman's rank correlation between the serum and abscess concentration was statistically significant (rs = 0.28, $P < 0.05$) suggesting that the higher the concentration of ethambutol in serum the higher would be the concentration in the cold abscess.

Reassessment after 3 to 5 months of triple drug therapy

In 4 patients in whom the concentration of drugs was reassessed, no significant change in the pattern of concentration was observed as compared with the pretreatment levels.

DISCUSSION

In the human clinical material there are a large number of variables such as site, duration, extent and pathological state of the lesion; age, nutritional status, metabolic behaviour of the patient; previous treatment, sensitivity and type of infecting organism. Earlier workers (Felländer et al. 1952, Katayama et al. 1954, Friedman & Kapur 1973) who tried to determine the concentration of streptomycin in tuberculous material in

human skeletal tuberculous lesions observed a wide variation in their results from patient to patient. Similar variations were observed in our study and that is why the data have been statistically analysed for clinical application and the range of concentrations has been mentioned.

Streptomycin concentration in the serum

Streptomycin does not penetrate the erythrocytes, therefore its concentration is approximately twice that in whole blood. The average serum concentration reported by various workers (Katayama et al. 1954, Barry 1964, Friedman & Kapur 1973) 3 hours after intramuscular injection of 1 g of streptomycin is estimated to range between 20 and 30 μg per ml approximately. The average serum concentration in our study was 23.34 and 13.47 μg per ml, in Group I and II, respectively. Overall comparison with other reports reveals similar concentrations in different races.

Streptomycin concentration in tuberculous material

Barry (1964) measured that almost 50 to 80 per cent of any drug would reach a tuberculous joint from the blood. Observations in the present report confirm this belief that streptomycin penetrates freely into the intra-articular compartments. The difference between the serum and joint concentrations in our study was statistically insignificant (median = 16, $x^2 = 0.1$, $P > 0.50$).

In the cold abscess, Katayama et al. (1954) measured 2.7 μg per ml of streptomycin 1½ hours after the administration of ½ g of streptomycin. Felländer et al. (1952) and Hever & Risko (1960) observed 2–4 μg of streptomycin 3 hours after the administration of 1 g of streptomycin. In the present series, although there was a wide variation in range (0.5–32.0 μg per ml), in the majority of the patients the concentration achieved in the abscess was much higher than the minimum inhibitory concentration (MIC) required for most types of human mycobacteria (MIC for most of Mycobacteria homonis = 1 μg per ml).

Ethambutol concentration in serum

After oral administration, this drug is readily absorbed and most of the drug circulates accumulated on the surface of the erythrocytes. It is rapidly excreted through the kidneys. Accumulation on the erythrocytes means that the concentration in the serum is almost half that of the whole blood. Most workers (Boborowitz 1966, Donomae & Yamamoto 1966, Gomez-Pimienta et al. 1966, Pyle et al. 1966) have reported the ethambutol concentration in the serum to range between 3 and 6 μg per ml under almost similar conditions. The concentration in the serum in the two groups in our series ranged from 1.2 to 16.0 μg per ml.

Ethambutol concentration in tuberculous material

Like streptomycin the average concentration of ethambutol in the joint aspirates (Group I; 3.41 μg per ml) was the same as that of the serum (median = 2, $x^2 = 0.05$, $P > 0.30$) thus suggesting free flow of the drug into the tuberculous joints.

In Group II, on the other hand, the concentration in the cold abscess (3.21 μg per ml) was about one third of the concentration in the serum (10.17 μg per ml). We could not obtain observations of other workers. The minimum inhibitory concentration of ethambutol for all varieties of mycobacteria is reported to be 1–4 μg per ml of the fluid, though most of the mycobacteria from human clinical tuberculous material are susceptible to 1 μg per ml of ethambutol (Lucchesi et al. 1966). Thus, even in Group II, the concentration of ethambutol in the

tuberculous pus was much higher than the required minimum inhibitory concentration of ethambutol for the infecting organisms. The majority of the skeletal tuberculous lesions are caused by the human type of mycobacteria which are expected to respond to concentrations of 1μg of ethambutol per ml.

Reports of other workers

It has been shown by various workers that radioactive dihydrostreptomycin (Andre 1956, Hanngren & Andre 1964, Lindberg 1967) and radioactive para-aminosalicylic acid (Hanngren 1959) reach skeletal tubercular foci. Radioactive isoniazid (Barclay et al. 1953, Canetti 1955) has been reported to diffuse freely into all tissues including bone, as well as into abscess cavities and even dried caseous material, in sufficient concentrations to destroy the bacteria. Tuli et al. (1974) reported that the concentration of streptomycin in experimental osseous tuberculous lesions after a single intramuscular injection (equivalent to a therapeutic dose) was much higher than that considered inhibitory to the human type of mycobacterium tuberculosis.

Therapy in clinical cases

In clinical practice as a rule more than one drug is administered over a period of time. Isoniazid, the most commonly used drug, has the property of causing vasodilation in the diseased area. Thus it may rationally be expected that the titre of concentration of the individual drugs would be much higher and the cumulative bacteriostatic/bacteriocidal effect would be much greater than that observed after limited doses of the drugs. It is clear that, irrespective of the precise pharmacodynamics, in clinical practice the concentrations achieved in skeletal tubercular lesions are in excess of the usually accepted inhibitory levels of the drugs to the mycobacterial organisms. It can be stated with certainty that if the organism is sensitive to the antitubercular drug and the drug is administered for a sufficient period of time, the infection may well be controlled and most of the lesions will heal. If a lesion does not come under control the cause is not failure of the drugs to reach the lesion in sufficient concentrations. The cause lies in other factors such as the nature of the mycobacterium (atypical, being generally resistant to first line drugs), the resistance of the infecting organism to the drugs being administered, and the mechanical nature of the pathology of the skeletal lesion, e.g., the presence of a large sequestra and areas of extensive destruction.

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