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Rifampicin in collections of pus – a kinetic study in human abscesses

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Most of the successful non-surgical management of abdominal abscesses is based upon the presence of therapeutic amounts of effective antibiotics within the collection. However few data are currently available concerning antimicrobial levels in human purulent lesions. To study the relationship between serum and pus concentrations of rifampicin, 11 patients with deep-seated abscesses were given 900 mg intravenously of rifampicin daily; after 3, 8 and 20 h from injection, an ultrasound-guided percutaneous aspiration of the collection was performed. Samples were obtained on the first day of therapy in six cases, while in other six the aspiration took place on the third day.

Rifampicin levels of therapeutic value were present after 8 h from the first injection. From this time antibiotic amounts in pus, ranging from 1·6 to 5·8 mg/l, were consistent with a long persistence of rifampicin in abscesses, without any evidence of accumulation.

Introduction

The main therapeutic goal while treating severe infections is to achieve stable concentrations of antibiotic, above the minimum bactericidal concentration (MBC), in body fluids, in target organs and in every site of suspected bacterial growth. While antibiotic levels in blood are currently monitored by commonly available methods, the scarcity of data on the concentration and activity of antimicrobials in pufulent collections is conceivably due to the lack of simple and reliable investigative methods; furthermore pus samples can be usually obtained from patients only by surgery or when a drainage is present. Recently, however, percutaneous aspiration has been widely employed for the non-surgical management of abdominal abscesses (Berger & Osborne, 1982), where this technique provides a harmless way to drain pus, isolate the causative organisms and inject antibiotics within the cavity.

This pilot study has been designed to assess antibiotic concentrations in purulent collections, using in all cases but one, real-time ultrasound equipment for carrying out percutaneous guided aspirations of deep-seated abscesses.

Rifampicin was chosen as the test antibiotic in this study since it shows a high diffusion through biological membranes, including cell-wall (Acocella, 1978), and since it maintains its activity even in pus, as experimental work on an *in-vitro* model (Bryant, 1979) or animal infection (Fu *et al.*, 1981) previously suggested.

Patients and methods

Eleven patients admitted to our Hospital from January to December 1982, were included in this study. All had a demonstrated pus collection of different shape and size not yet treated with antimicrobials.

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In six cases the abscess was located in the liver (four bacterial; two amoebic); in four there was an intraperitoneal collection (two after cholecystectomy and one each after hysterectomy and hemicolectomy); the remaining patient was suffering from a subperiosteal abscess as the result of a post-traumatic osteomyelitis of the femur. Ultrasound-guided percutaneous aspiration (employing Aloka SSD 240 real-time equipment) was the draining procedure in all the abdominal cases, according to the technique described elsewhere (Holm *et al.*, 1973).

In one case of bacterial origin the liver was punctured twice (patient no. 3). All patients were given a daily intravenous dose of 900 mg of rifampicin, diluted in 500 ml of 5% glucose injected over 2 h, provided in injectable form by Lepetit S.p.A., Milan, Italy. Rifampicin levels were determined in pus and simultaneously in serum and saliva in three groups of two patients each, respectively 2, 8 and 20 h after the end of the first infusion. Three other corresponding groups of two patients each were sampled 2, 8 and 20 h after the third administration. Serum and saliva were tested directly after collection, whereas pus specimens, if not grossly contaminated by blood, were stored at −20 °C until used. After thawing, pus was diluted with equal amounts of distilled water and incubated for half an hour at room temperature.

After that the sample was mixed (Vortex mixer) and centrifuged at 4000 rpm for 5 min, the supernatant was taken for the agar well diffusion assay. Antibiotic levels were determined microbiologically with *Sarcina lutea* ATCC 9341 as test organism, according to the method described by Sabath & Matsen (1974).

Results

The determinations are summarized in Table I and, for pus and serum, the corresponding mean values are also outlined in Figure 1. While salivary concentrations were negligible (never above 0·7 mg/l) in agreement with literature data, the comparison between rifampicin levels in pus and serum provides information of therapeutic interest. Concentrations in pus measured 3 h after the injection were higher on day 3 than after the first administration; at the same time rifampicin concentrations in serum were larger in the two patients punctured on day 1 than in the corresponding two sampled on day 3. At the eighth hour the rifampicin concentration in pus was almost the same on day 1 and 3, and only a small difference from the relative serum concentration is shown.

After 20 h, whereas antibiotic is at its lowest levels in blood, its amount in pus was still close to 8 h values and there was no significant differences between day 1 and 3 determinations.

Discussion

Effective treatment of severe infections may be variously hampered by the presence of purulent collections, which act as sanctuaries for causative pathogens. Many factors account for bacterial survival in pus, despite the presence of adequate antibiotic levels in blood. Erratic entry of a given antimicrobial into these collections is only one of these factors causing an impaired therapeutic response. Investigators have also drawn attention on the viability of bacteria inside phagocytes and have emphasized the role of low pH, decreased pO_2, local degradation, inactivation and binding of antibiotic that, along with other environmental changes, take place in abscesses (Bryant & Hammond, 1974).

The lack of reliable and easily reproducible *in-vitro* tests for the study of antibiotic kinetics and activity in pus provides further uncertainty concerning the real effectiveness

Table I. Rifampicin levels after 900 mg intravenous infusion daily

Patient no.	Time of sample (h)	Concentration of rifampicin (mg/l) in Pus	Serum	Saliva
Investigation on first day				
1	3	0·1	12·5	0·35
2	3	0·26	17·0	0·1
3	8	3	5	0·28
4	8	1·8	2·4	0·4
5	20	1·6	0·18	0·1
6	20	2·4	0·1	0·1
Investigation on third day				
7	3	3·2	6·8	0·7
8	3	5·6	9·4	0·38
3	8	3·6	5·0	0·2
9	8	2·4	3·0	0·15
10	20	2·4	0·1	0
11	20	5·8	0·1	0·1

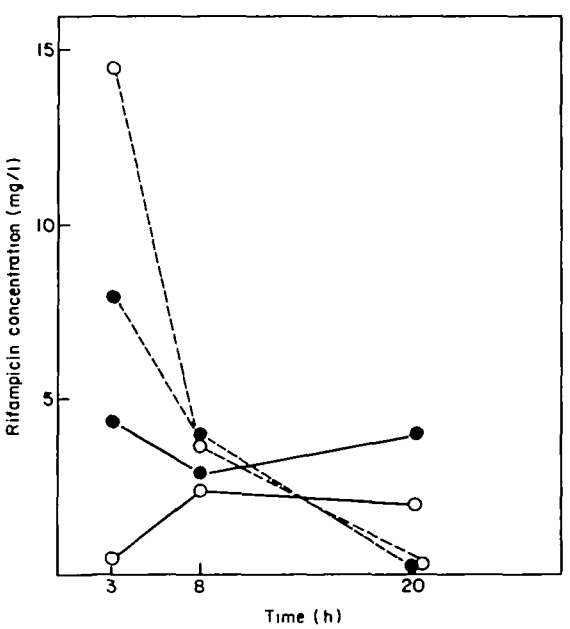

Figure 1. Rifampicin mean concentration in pus and serum, obtained at indicated times on day 1 and 3, after intravenous infusion of 900 mg of rifampicin. ——, Pus; – – –, serum; ○, day 1; ●, day 3.

of an antibacterial drug once administered to a patient with purulent lesions; animal data may be of help, but it is questionable if such findings can be completely transposed to humans.

All patients enrolled in this study were given rifampicin, since this drug is reportedly

effective for the treatment of patients with deep-seated abscesses (Lobo & Mandell, 1972) and recent papers testify to a growing interest for its use other than in tuberculosis (Leading article, 1976). Rifampicin indeed has good phagocyte penetration unrelated to cell viability (Prokesch & Hand, 1982) and is able to kill intraleukocytic pathogens, such as staphylococci (Mandell & Vest, 1972), that may be involved in abscess formation.

As described in Methods, rifampicin was administered intravenously as monotherapy for a maximum of three days, since the fast development of bacterial resistance suggests this drug should be used in combination with other antimicrobials (Faville *et al.*, 1978). After the percutaneous drainage, susceptibility tests performed on the bacterial isolates indicated the most suitable antibiotic therapy. The two cases of amoebic abscesses were treated with rifampicin before that serology and ultrasonic-guided puncture itself gave evidence concerning the lesion origin; both these cases underwent evacuation after a single rifampicin administration.

Our data show good diffusion of rifampicin into purulent collections where, after 8 h from the first injection, it reaches levels higher than the MBC of most Gram-positive pathogens. The rate of penetration of rifampicin into abscesses may be deduced from the comparison between pus and serum levels at the third and eighth hour on the first day: high serum values at the third hour (12·5 to 17 mg/l) have corresponding low amounts in pus (0·35 to 0·1 mg/l); eight-hour levels in pus, however, show that rifampicin, at this time, has already attained therapeutic concentrations (5 to 2·4 mg/l). Concentrations in pus obtained at the third hour on day 3 are consistent with long persistence of the antibiotic in these lesions, as other values at other times show as well. Furthermore there is no evidence of accumulation and rifampicin levels in pus are never above 6 mg/l. The data obtained in patient no. 3 punctured twice at the eighth hour on day 1 and 3, further confirm this kinetic trend. In conclusion this study confirms rifampicin's ability to enter and stay in purulent lesions but an increase in patient numbers and, perhaps, a different choice of collection times should be designed. This will give a more accurate concentration-time curve and also valuable information about the persistence of rifampicin in the abscesses.

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