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Concentrations of some antibiotics in synovial fluid after oral administration, with special reference to antistaphylococcal activity

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SUMMARY One of 4 antibiotics with antistaphylococcal activity was given in a conventional oral dose for one day to each of 20 hospitalised patients with synovial effusion of a knee joint requiring aspiration. Serial synchronous samples of serum and synovial fluid (SF) were taken over 36 hours through indwelling cannulae. No morbidity was experienced either during or after this procedure. Satisfactory antistaphylococcal concentrations in SF were achieved with sodium fusidate (500 mg 8 hourly) and amoxycillin (250 mg 8 hourly). Cephradine (500 mg 6 hourly) frequently failed to reach the minimum inhibitory concentration for *Staphylococcus aureus* in the SF, and flucloxacillin (250 mg 6 hourly) was unpredictable in its penetration of the synovial space. Wide interpatient variation of both serum and SF concentrations was found. Our results indicate that sodium fusidate is an appropriate early treatment for a nonresistant staphylococcal joint infection. Amoxycillin is a suitable alternative or second antistaphylococcal drug and would also be appropriate initial therapy when the infecting organism is unknown. We strongly recommend that SF antibiotic concentrations be measured, to ensure adequate penetration of the synovial cavity, in the treatment of septic arthritis.

Septic arthritis is an important complication of pre-existing joint disease, especially rheumatoid arthritis.[1-3] Since Kellgren and his colleagues[4] first emphasised the morbidity and potential high mortality of pyogenic infection of rheumatoid joints about 100 cases have been reported in the English language literature. Such infection should always be suspected when a patient with rheumatoid arthritis has one disproportionately inflamed joint or is inexplicably ill. Septic arthritis may complicate other forms of arthritis. It also occurs in nonrheumatic conditions liable to secondary infection such as diabetes mellitus, leukaemias, or lymphomas, and in those taking corticosteroid, immunosuppresive, or cytotoxic drugs.[5] It may occur in any septicaemic or bacteraemic state,[6 7] including drug addicts,[8] or in chronically ill elderly individuals.

Staphylococcus aureus is by far the most common organism causing septic arthritis, and this is often penicillin resistant. Many other bacteria have also been incriminated, including streptococci, pneumococci, *Haemophilus influenzae*, neisseria, *Escherichia coli*, and bacteroides.[10-12] Antibiotic therapy is theoretically curative but must be given promptly in adequate doses to prevent long-term morbidity or mortality. Parenteral (intravenous) administration is preferred by some in the initial stage.[13] The intra-articular route has also been advocated but is not devoid of complications, including chemical synovitis.[14] Practical considerations make it desirable to use the oral route for the later and often protracted phase of treatment.

Insufficient information is available about the maintenance of adequate inhibitory concentrations of most antibiotics in synovial fluid after either parenteral or oral administration. Sequential assays of synovial fluid concentrations have been reported only on infrequent samples with very few antibiotics.[15-22] We therefore devised a method for frequent sampling of synovial fluid synchronously with blood in patients with knee joint effusion in order to ascertain the relative concentrations, at frequent time intervals, during one day's administration of antibiotics in recommended oral doses.

We also assessed the severity of inflammation in order to correlate this with the time scale and degree of antibiotic penetration of the synovial space and to compare it with similar assays in relatively non-inflamed joints. We chose 4 antibiotics of which 2

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Table 1 *Clinical and laboratory data from 20 patients*

Patient	*Age*	*Sex*	*Diagnosis*	*Inflammatory indices (clinical)*				*ESR*	*Protein (SF)*	*Cells (SF)*		*Antibiotics*
				Swelling	*Tenderness*	*Pain*	*Warmth*		*g/l*	*Total*	*% Polymorphs*	
1	51	F	RA	3	4	3	3	61	53	17 000	66	A
*2	24	F	RA	4	3	4	3	44	58	16 800	82	C
				3	2	3	3	34	50	13 400	65	NaF+Flu
*3	55	F	Rheumatoid factor	4	4	4	4	61	125	13 200	71	NaF+Flu
			neg. †	4	4	3	2	40	95	9 500	60	A
4	61	M	RA	4	4	4	4	70	48	12 000	79	A
5	58	F	RA	4	4	3	3	78	42	28 900	87	C
6	68	F	Polyarthritis + OA	4	4	4	4	42	49	2 300	61	NaF
7	70	F	OA	4	2	3	2	18	43	12 000	65	C
8	46	M	Monoarthritis	4	2	2	2	2	40	4 100	60	A
9	80	F	RA	4	4	4	3	59	49	3 700	95	A
*10	44	M	PVNS	4	3	2	2	1	36	2 100	27	C
				3	2	2	2	1	26	1 600	24	NaF
11	63	M	RA	4	4	3	3	57	50	11 700	49	C
12	72	F	OA + traumatic synovitis	4	2	3	1	11	34	3 600	60	C
13	80	F	RA + OA	4	4	4	3	81	39	6 300	37	Flu
14	51	F	OA	4	2	2	2	6	42	400	2	NaF
15	61	M	RA	4	4	3	4	74	46	11 400	76	Flu
16	32	M	Monoarthritis	4	3	4	4	32	38	6 000	45	A
17	59	F	RA	4	4	3	3	43	44	8 200	25	A
18	23	F	Psoriatic arthritis	3	4	4	3	58	35	15 000	66	Flu
19	38	M	PVNS	3	2	2	2	25	38	4 000	68	Flu
20	61	M	RA	4	4	3	3	68	50		70	NaF

A = amoxycillin. C = cephradine. Flu = flucloxacillin. NaF = sodium fusidate.

*Patients used for 2 experiments on different occasions (same knee joint with 6–8-week intervals).

† Rheumatoid factor negative inflammatory arthritis associated with HLA B27.

(sodium fusidate and flucloxacillin) were developed for their antistaphylococcal effect, and the others (amoxycillin and cephradine) had a wide antibacterial, including antistaphylococcal, spectrum of activity.

Patients and methods

Twenty patients (8 males, 12 females) entered this study (Table 1). Their ages ranged from 24 to 80 years, with a mean age of 45. All patients had knee joint effusions requiring diagnostic or therapeutic aspiration, and included inpatients and outpatients attending the rheumatology department. Twelve of the effusions were due to RA as defined by the diagnostic criteria of the American Rheumatism Association 1959[23] or to other inflammatory arthropathies. Four subjects had osteoarthrosis, as diagnosed by clinical features, characteristic radiological findings, normal ESR, and negative tests for rheumatoid factor, and 2 other patients had pigmented villonodular synovitis (PVNS). These 6 patients could be considered to have effusions which were not primarily inflammatory in origin, and they therefore provide a comparison with patients suffering from inflammatory effusions.

The nature of the investigation was explained to each subject, who underwent a general medical examination and a detailed examination of the musculoskeletal system, including local assessment of the knee joint for swelling, tenderness, warmth, and range of movement, all of which were assessed semiquantitatively on a 0–4 scale. The general inflammatory state was quantified by conventional clinical and laboratory parameters, including the articular index of Ritchie *et al.*,[24] a full blood count, ESR, and joint radiographs. Synovial fluid (SF) from the knee joint was examined for total and differential cell count and albumin and globulin concentrations (Table 1). Pre-existing antirheumatic medication was continued unchanged.

Each individual was confined to bed for 72 hours, with the knee resting in a plaster-of-Paris back splint. Under conventional asepsis, a size 16 Angiocath and a Venflon plastic cannula were inserted into the knee and a forearm vein respectively and left in situ for 36 hours. No morbidity was experienced either during the investigation or at a subsequent 6-months follow-up period. Patients with clinical or biochemical evidence of hepatic or renal disease, those with hypersensitivity to penicillin or other antibiotics, and pregnant women were excluded from the study.

Of the 4 antibiotics examined 2, sodium fusidate and flucloxacillin, are recommended for staphylococcal infection, and 2 others, amoxycillin and cephradine, have a wide spectrum of antibacterial, including antistaphylococcal, activity.

Patients were given one or 2 of these antibiotics in conventional dosage by mouth for one day, as follows: amoxycillin 250 mg 8 hourly, 7 subjects; cephradine 500 mg 6 hourly, 6 subjects; flucloxacillin 250 mg 6 hourly, 6 subjects; sodium fusidate 500 mg 8 hourly, 6 subjects.

Samples of blood (5 ml) and SF (2 ml) were withdrawn immediately before the first dose of antibiotic and then at 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 12, 24, and 36 hours thereafter. After centrifugation the SF and plasma were stored at −70°C until assay. Antibiotic levels were measured by standard agar diffusion microbiological assay.[25] Methods used were generally those recommended by the manufacturers, who also provided purified antibiotics used for making standard solutions.

Amoxycillin (Bencard), cephradine (Squibb), and flucloxacillin (Beecham) were assayed on plates flooded with a suspension of *Sarcina lutea* (NCTC 8340), the samples being contained either in wells in the agar (amoxycillin) or in stainless steel cylinders resting on the surface of the agar (cephradine and flucloxacillin). Sodium fusidate (Leo Laboratories) was assayed on plates seeded with *Corynebacterium xerosis* and samples were placed in the agar. Two of the earlier patients received both sodium fusidate and flucloxacillin, and it was necessary to remove the antibacterial effects of the second agent when performing the assay in these cases. Flucloxacillin was inhibited by beta lactamase (Whatman) derived from *Bacillus cereus* at 10 units/ml final concentration, and the action of fucidic acid was overcome by use of a strain of *Sarcina lutea* (NCTC 8340) trained to a high degree of resistance to this agent. In these cases appropriate controls were included to demonstrate any inhibition due to the other simultaneously administered antibiotic. As a check against blood contamination of SF samples those which were pink tinged were measured spectrophotometrically at 560 nm. The haemoglobin content thus determined was never greater than 1%

Results

The concentrations of the antibiotics in both serum and SF are shown in Figs. 1–5. Figs. 1–4 show serum and SF antibiotic concentrations as the mean results from 6 patients in each group (with the exception of amoxycillin, which has 7 patients), together with individual results in SF. Fig. 5 shows the range of serum concentrations for amoxycillin as an example of the wide scatter of individual serum concentration found with all 4 antibiotics. The scatter of results rendered standard deviations for serum or SF concentrations of little value, and thus we have not recorded them here.

Peak serum concentrations for all antibiotics occurred in most subjects between $1\frac{1}{2}$ and $2\frac{1}{2}$ hours. Less frequent sampling later in the experiments failed to coincide with further peak levels but probably indicates approximate trough levels between doses. Peak concentrations in SF occurred slightly later than in serum, and the rate of fall mirrored that of serum levels.

The individual SF antibiotic concentrations following the first dose, at least in the case of amoxycillin and sodium fusidate, adequately exceeded the minimum inhibitory concentration (MIC) of *Staph. aureus*. Sodium fusidate in particular exceeded this value in both serum and SF by a wide margin. In addition, there also appears to be a trend towards accumulation of this antibiotic in blood and SF.

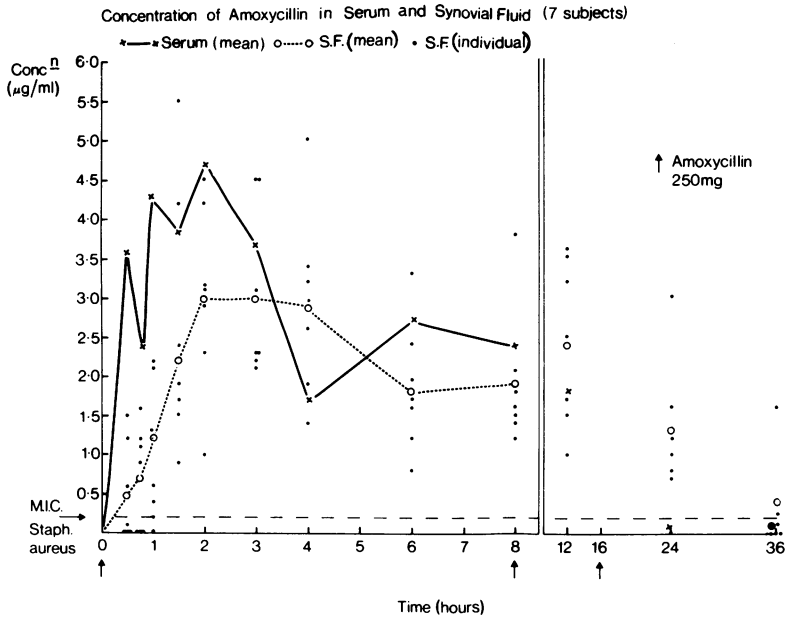

Fig. 1 *Mean serum and synovial fluid together with individual synovial fluid concentrations of amoxycillin after oral administration (7 subjects).*

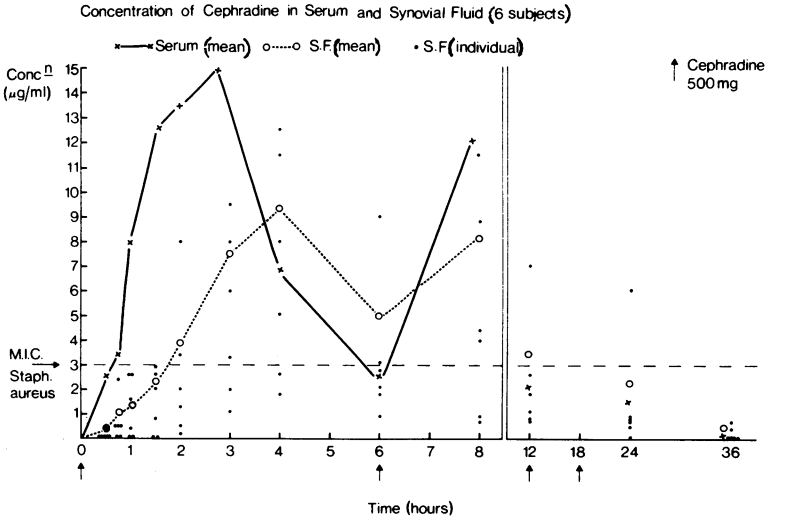

Fig. 2 *Mean serum and synovial fluid together with individual synovial fluid concentrations of cephradine after oral administration (6 subjects).*

The individual results with flucloxicillin and cephradine were less favourable. Although flucloxacillin achieved satisfactory SF levels in some patients, mean SF concentrations were well below the serum levels and not greatly in excess of the MIC for *Staph. aureus*. Examination of the individual results showed a wide variation between patients, with no measurable concentrations in SF in a substantial proportion. In the case of cephradine, although most levels adequately exceeded the MIC for *Staph. aureus* in serum, they did not do so in SF, and the individual results, as with flucloxacillin, were unpredictable.

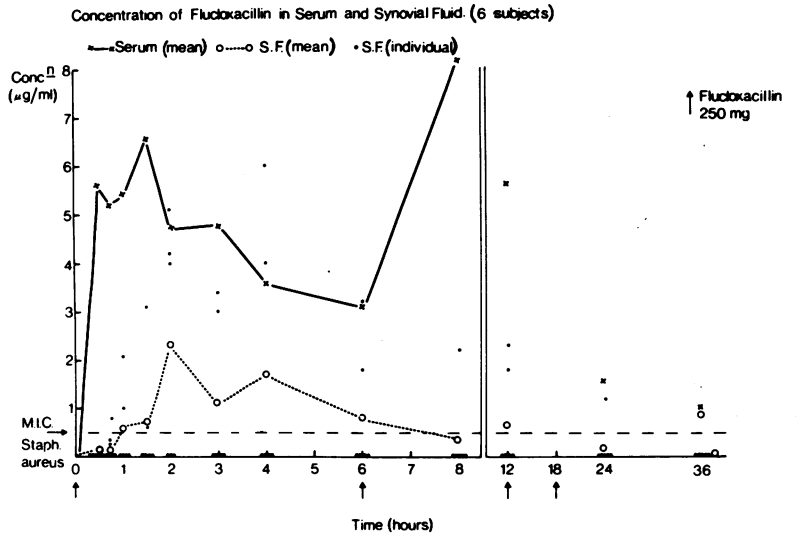

Fig. 3 *Mean serum and synovial fluid together with individual synovial fluid concentrations of flucloxacillin after oral administration (6 subjects).*

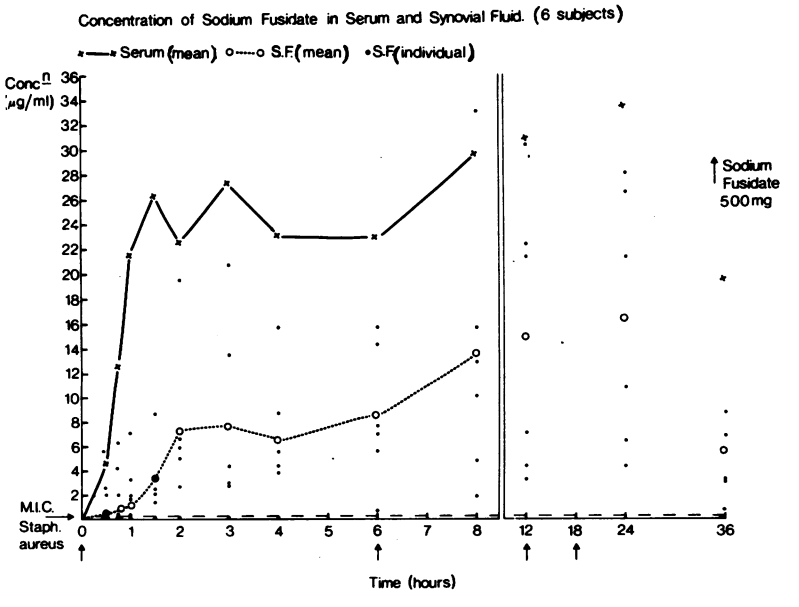

Fig. 4 *Mean serum and synovial fluid together with individual synovial fluid concentrations of sodium fusidate after oral administration (6 subjects).*

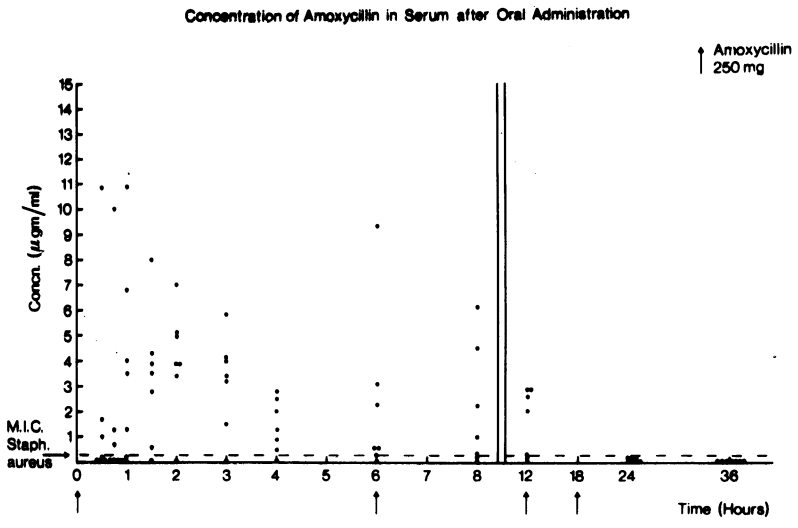

Fig. 5 *Concentrations of amoxycillin in serum after oral administration (7 subjects).*

Wide interpatient variation was found in serum and SF with all 4 antibiotics, apparently independent of underlying pathology or severity of inflammation, and no correlation was found between SF concentrations and clinical or laboratory indices of inflammation (Table 1).

Discussion

Antibiotic concentration in joint fluid must be considered in relation to the concentration needed to eliminate a pathogen. The World Health Organisation (WHO) recommends that the antibiotic concentration should exceed the MIC of the organism by a margin of 2- to 4-fold to ensure that the infection is amenable to treatment.[26]

It can be seen from the above results that sodium fusidate and amoxycillin rapidly enter the joint fluid of inflamed joints after oral administration in the doses we selected, and these levels approach those in the plasma and are in excess of the in-vitro MICs of those bacteria commonly responsible for pyogenic infection. The SF concentrations of cephradine and flucloxacillin were often inadequate with the doses we employed. Flucloxacillin was unpredictable as to its penetration of SF, achieving concentrations sufficiently in excess of the MIC for *Staph. aureus* in only a minority of subjects. Cephradine penetrated poorly into the SF in some cases and was clearly unsatisfactory in this regard. These results also show that concentrations of antibiotics in SF reach peak levels rather later than in serum and decrease more slowly, and that there are appreciable amounts present in joint fluid up to 12 hours after the last dose of antibiotics, as previously reported from various studies with penicillin in the 1940s.[27-29] Our study confirms the results of previous workers that with the possible exception of sodium fusidate, which has an enterohepatic recirculation, there is with these doses no accumulation of antibiotics in joint fluid, although they disappear more slowly than from the serum. Our study also demonstrates wide interpatient variability in the joint fluid antibiotic concentrations as well as changes related to time and dosage. This is a reflection of wide variation in serum concentrations, a common finding in pharmacokinetic studies with many antibiotic compounds. Most previous studies described single or very few determinations of antibiotic concentrations following parenteral administration, and those do not necessarily reflect either maximum or average concentrations Sequential samples such as we have collected over a relatively long period provide a more detailed view of the ongoing concentration in the joint cavity.

Trough levels of cephradine and flucloxacillin, just before the later doses, show concentrations below the MIC of *Staph. aureus* and most other pathogenic organisms, indicating that these antibiotics are probably unsuitable for the treatment of staphylococcal joint sepsis, at least in conventional dose ranges. Sodium fusidate and amoxycillin on the other hand, achieved good penetration with concentrations well in excess of the MIC for *Staph. aureus.*

In plasma, antibiotics are variably protein bound, mainly to albumin (sodium fusidate 95%, flucloxicillin 90%. amoxycillin 20%, and cephradine 5%). Serum and SF protein changes are well recognised abnormalities in RA and other inflammatory arthropathies,[30] and SF antibiotic levels could conceivably be substantially dependent on this increase in

proteins. However, in our study we have found no correlation between SF proteins and antibiotic concentrations, which varied independently of the severity of the inflammation, as measured either clinically or by laboratory criteria (Table 1).

Our results lend some support to the findings of previous workers[31 32] that high protein binding may impair penetration into SF in that the highly bound flucloxacillin and sodium fusidate achieved a lower proportional penetration relative to serum concentration than did the less highly bound amoxycillin and cephradine. However, it is clear that this factor is less important than is the intrinsic antibacterial activity of the drug. Thus the concentration of sodium fusidate exceeded the MIC of *Staph. aureus* by a factor of more than 100, whereas that of cephradine exceeded it only approximately 2-fold.

On the basis of the foregoing it appears that oral sodium fusidate is an appropriate initial treatment for a nonresistant staphylococcal joint infection. Unfortunately resistance to this agent may develop during the course of treatment, and it is common practice to combine this antibiotic with a second antistaphylococcal drug.[33] In the case of a penicillin sensitive staphylococcus previously published work suggests that penicillin G may be used as the drug of first choice.[22 27-29] Amoxycillin or ampicillin penetrate well and are broad spectrum antibiotics which have a useful antistaphylococcal activity. Such drugs would serve as second antistaphylococcal agents or as a first-line drug if the nature of the infection is not known.

We recommend that estimation of SF antibiotic concentrations be performed where possible to ensure adequate concentration in the joint. Whether or not this estimation is practicable, it is probably advisable to administer antibiotics parenterally in the early stages of the infection[12 33-35] or orally in doses greater than usually recommended.

Finally, we have described a safe, painless method for continuous sampling of synovial fluid from the knee joint over periods of up to 36 hours, which may have other applications in the study of joint physiology and pathology.

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