The penetration of metronidazole into synovial fluid

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Summary

Six patients with non-infected synovial effusions, associated either with inflammatory or degenerative arthropathy and requiring diagnostic or therapeutic aspiration, were given a short course of 400 mg metronidazole (Flagyl) 8-hourly for 3 doses. Serum and synovial fluid (SF) were sampled frequently during this time, and assayed for metronidazole by a specific high pressure liquid-chromatographic method. It was found that concentrations of metronidazole in SF reached those in serum after a short time-lag, and thereafter approximated to the serum concentration. With this regimen, metronidazole concentrations were readily achieved in synovial fluid, above the minimum inhibitory concentrations for most susceptible anaerobes. These results indicate that the drug freely enters the synovial fluid and suggests that metronidazole would prove effective in the treatment of septic arthritis due to anaerobic bacteria.

Introduction

Septic arthritis is an important complication of inflammatory joint diseases and particularly of rheumatoid arthritis (Kellgren *et al.*, 1958). Pyogenic infection of a synovial joint is rarer today than in the past, but is still seen frequently enough to constitute a problem of diagnosis and treatment. Sepsis may also complicate non-rheumatological diseases, such as diabetes, leukaemias, lymphomas, any debilitating condition (Douglas, Lewin and Sokoloff, 1964; Rimoni and Wennberg, 1966), and also those diseases treated with immunosuppressants and cytotoxic drugs (Douglas *et al.*, 1964).

Staphylococcus aureus is by far the most common infecting organism. However, many other organisms may also infect joints, and these include *Strepto-*

coccus, *Pneumococcus*, *Haemophilus influenzae*, *Pseudomonas*, *Salmonella*, *Klebsiella-Aerobacter* spp., *Proteus*, *Escherichia coli* and *Bacteroides*. Although anaerobic infection of joints is an uncommon event, it should still be considered a possibility when a patient develops a pyoarthrosis, especially after a severe fulminating chest or gastrointestinal or a genito-urinary tract infection (Zimmet, Davis and Firegold, 1969), particularly in those patients with an impaired immune response and those being treated with corticosteroids and other immunosuppressant agents.

Although the pharmacokinetic aspects of metronidazole have been studied intensively, using plasma or serum (Houghton *et al.*, 1979a, b; Bergan and Arnold, 1980; Amon *et al.*, 1981), and it has been shown that the drug is present in cerebrospinal fluid (Barling and Selkon, 1978) and saliva (Kaye, Sankey and Thomas, 1980), nothing is known of the ability of this antibiotic to permeate the synovial fluid (SF). Therefore, it was considered pertinent to investigate the permeability of the synovial cavity to metronidazole, because of its relevance to the treatment of joint sepsis due to anaerobic organisms (Eyky, 1979).

Metronidazole is considered to be an anaerobic agent, and is widely used both for the prophylaxis and treatment of anaerobic bacterial infections. The aim of this investigation was to study the time course and degree of penetration of this drug into the synovial cavity after its oral administration in order to ascertain whether adequate therapeutic concentrations can be achieved in SF with conventional doses.

Patients and methods

The 6 patients (2 males and 4 females) in this

study had non-infected synovial effusions, associated either with inflammatory or degenerative arthrosis, requiring diagnostic or therapeutic aspiration. They comprised in-patients and out-patients attending the Rheumatology Department of Southampton General Hospital. Their ages ranged from 28 to 74 years. Four patients had rheumatoid arthritis as defined by the diagnostic criteria of the American Rheumatism Association (Ropes *et al.*, 1958), one had osteoarthritis and the remaining patient had pigmented villonodular synovitis (PVNS).

Each subject underwent a general medical examination and a detailed examination of the musculo-skeletal system, including a local assessment of the knee joint using a semi-quantitative scale (0-4) for swelling, warmth, tenderness and range of movement. The inflammatory state was quantified by conventional clinical and laboratory parameters including the articular index of Ritchie *et al.* (1968), full blood count, ESR, titre of rheumatoid factor and antinuclear factor and synovial fluid analysis for cell count and protein concentrations.

Patients with hypersensitivity to penicillin and other antibiotics and also those with clinical or biochemical evidence of hepatic or renal disease were excluded from the study. Subjects were confined to bed with the knee resting in a plaster-of-Paris back splint. Under strict asepsis soft plastic (Angiocath-16 gauge) and venflon plastic cannulae were inserted into the knee joint and a suitable forearm vein respectively, and left *in situ* for 36 hr, using the method which is reported elsewhere (Sattar *et al.*, in press). No morbidity was experienced either during the investigation or in the subsequent 6-month follow-up period. Each patient was prescribed oral metronidazole (Flagyl) 400 mg 8 hourly for 3 doses. Samples of venous blood (5 ml) and synovial fluid (2 ml) were withdrawn at 0, 30, 45, 60, and 90 min and 2, 3, 4, 6, 8, 12, 24 and 36 hr after administration of the first dose. After centrifugation, samples of serum and SF were stored at -70°C until assayed. A specific high pressure liquid chromatographic method was used as previously described (Kaye *et al.*, 1980) to measure the level of metronidazole and its oxidative metabolite, 20396 RP [1 - (2 - hydroxyethyl) - 2 - methyl - 5 - nitroimidazole], which also has some anti-anaerobic activity.

Results

Illustrated in Fig. 1 are the mean concentrations of metronidazole and its metabolite achieved in the 6 patients up to 6 hr after the first dose of Flagyl. Table 1 shows detailed results over 36 hr, and it can be seen that the concentrations of the metabolite 20396 RP were much lower than those of metronida-

FIG. 1. Mean concentrations of metronidazole (■) and 20396 RP (●) in serum (—) and synovial fluid (---) samples obtained up to 6 hr after the oral administration of 400 mg of metronidazole (6 subjects).

zole for most of the study. It is evident that metronidazole has adequately penetrated into the synovial cavity where its concentration approximates to that in serum after a short time-lag. The decline of metronidazole concentrations in SF mirrored that in serum. The individual SF concentrations of metronidazole following the first dose are shown in Fig. 2, and adequately exceeded the minimum inhibitory concentration (MIC) of susceptible anaerobes, particularly of *B. fragilis*, of about $6\text{ }\mu\text{g/ml}$ (Brogden *et al.*, 1978). Examination of the individual results showed a wide inter-patient variation, both in serum and SF concentrations of metronidazole, a common finding in pharmacokinetic studies with many antibiotic compounds, which may be independent of underlying pathology or severity of inflammation.

Table 1 also shows mean concentrations of metronidazole in the 6-hr samples lower than those at 8 hr, suggesting that some patients inadvertently received the second dose of metronidazole before the designated time of 8 hr after the first dose. The concentrations of the metabolite were much lower than those of metronidazole for most of the study.

Illustrated in Fig. 3 is the relationship between serum and SF concentrations of metronidazole in the 24- and 36-hr samples obtained from the 6 patients. These time periods have been chosen to allow equilibration to be reached, and also to give

TABLE 1. Mean ($\pm$ s.d.) concentrations of metronidazole and its major oxidative metabolite, 20396 RP, in samples of serum and synovial fluid collected from 6 subjects at various time intervals after the oral administration of metronidazole 400 mg $\times$ 3 doses at 8-hourly intervals

Time (hr after first dose)	Drug concentration (μ g/ml)			
	Serum		Synovial fluid	
	Metronidazole	20396 RP	Metronidazole	20396 RP
0	n.d.	n.d.	n.d.	n.d.
0.5	3.6 (4.2)	0.2 (0.3)	0.7 (0.6)	n.d.
0.75	4.9 (4.2)	0.2 (0.3)	1.5 (1.4)	0.1 (0.1)
1	5.4 (3.7)	0.4 (0.3)	2.7 (2.3)	0.1 (0.2)
1.5	6.0 (3.4)	0.5 (0.4)	3.8 (2.9)	0.2 (0.3)
2	5.7 (3.7)	0.6 (0.5)	4.5 (2.8)	0.3 (0.3)
3	5.7 (2.7)	0.7 (0.5)	5.3 (3.2)	0.5 (0.5)
4	5.4 (0.8)	0.9 (0.5)	5.7 (2.6)	0.8 (0.6)
6	4.9 (1.5)	1.1 (0.4)	5.4 (1.8)	1.1 (0.6)
8	8.3 (5.9)	1.7 (0.9)	7.6 (2.8)	1.5 (0.5)
12	9.1 (3.7)	2.3 (0.8)	9.6 (2.4)	2.2 (0.8)
24	6.3 (1.6)	3.0 (1.1)	8.3 (2.2)	3.3 (0.8)
36	2.4 (1.9)	1.8 (0.5)	3.6 (2.8)	1.9 (1.0)

n.d.=not detected, i.e. concentration was $<0.05 \mu$ g/ml.

FIG. 2. Concentrations of metronidazole in synovial fluid after oral administration (6 subjects).

some indication of what might occur during longer term therapy. A close correlation between metronidazole concentrations in serum and SF is shown.

Discussion

As in the case of bone infections, anaerobes appear to be infrequently involved in pyogenic arthritis. *B. fragilis* is the most common anaerobic bacterium isolated from human infections, and has been

implicated as a cause of pelvic, intra-abdominal, pleuro-pulmonary and soft tissue infections, brain abscess, endocarditis, septic arthritis, osteomyelitis and septicaemia (Heinemann and Braude, 1963; Ledger *et al.*, 1975; Nettles *et al.*, 1969; Swartz, 1970; Zinmet *et al.*, 1969; Felner and Dowell, 1970; Bartlett and Finegold, 1972; Chow and Guze, 1974; Gorbach and Bartlett, 1974). Zinmet *et al.* (1969) reviewed the world literature and found 47 cases of

septic joint infections involving anaerobic bacteria. Most of these reported cases were from the pre-antibiotic era and were associated with fulminating upper respiratory infections accompanied by *Fusobacterium necrophorum*, *Peptostreptococcus* and *Clostridium*. However, the authors have observed 2 patients with septic arthritis due to *B. fragilis* complicating rheumatoid arthritis. Haematogenous seeding appears to be the most common mode of anaerobic joint sepsis.

FIG. 3. Relationship between serum and synovial fluid concentrations of metronidazole in the 24- and 36-hr samples obtained from 6 subjects after oral administration of 400 mg metronidazole at approximately 8-hourly intervals $\times 3$.

Until 1959, when metronidazole was introduced to clinical medicine for the treatment of *Trichomonas vaginalis* infection, penicillin was considered to be the drug of choice in the treatment of anaerobic infections except those due to *B. fragilis* (Tally, Sutter and Finegold, 1975). Subsequently, for infections occurring below the diaphragm either clindamycin or chloramphenicol were recommended, whereas in most infections above the diaphragm penicillin remained the accepted agent. More recently, clindamycin has superseded chloramphenicol for anaerobic infections because of the potential toxic effects of the latter drug. However, the use of clindamycin has been reported to lead to pseudomembranous enterocolitis (Cohen, McNeil and Wells, 1973; Wells, Cohen and McNeil, 1974; Hubbard, 1974) and also some anaerobes have been

found to be resistant to this drug (Bartlett *et al.*, 1973; Wilkins and Thiel, 1973). The effectiveness of clindamycin against Gram-negative anaerobes has been demonstrated (Bartlett and Finegold, 1972) and these authors also described metronidazole as an anaerobic agent having bactericidal activity against *B. fragilis* (Finegold *et al.*, 1975).

It can be seen from the above results that metronidazole rapidly entered the synovial fluid of inflamed joints following the oral administration of 400 mg metronidazole, 8-hourly as Flagyl. Concentrations in serum and SF reached optimum therapeutic levels and were above the MIC of most susceptible anaerobes, particularly *B. fragilis*. After a short time-lag, the concentrations of metronidazole in SF approximated to those achieved in serum, and were in excess of the *in vitro* values required to eliminate those anaerobes likely to be responsible for joint and bone infections.

Antibiotic concentrations in joint fluid must be considered in relation to the concentration required to eliminate a pathogen. Very few studies have been published on the penetration of antibiotics into the effusion of infected joints, most of the reports being concerned with non-infected effusions. However, it is reasonable to assume that the permeability of the synovial membrane is similar, whether the inflammation is due to bacterial infection or to other causes. If this is the case, the concentrations of metronidazole obtained in this study would also be achieved in the effusions present in an infected joint. It is interesting to note that some other antibiotics, notably flucloxacillin and cephadrine often failed to achieve satisfactory concentrations in synovial fluid in conventional oral doses (Sattar, Barrett and Cawley in press).

In view of the present findings, that concentrations of metronidazole in synovial fluid are approximately the same as those in serum and in excess of the MIC for most susceptible anaerobes, this drug should be of value in the treatment of septic arthritis due to anaerobic bacteria, and especially *B. fragilis*. This view is supported by the successful elimination of *B. fragilis* from the knee joint of a patient with septic arthritis complicating severe rheumatoid arthritis under the care of one of the authors (M.I.D.C.).

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