Clindamycin levels in sputum in a patient with purulent chest disease due to cystic fibrosis

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Most workers agree that the ability of an antibiotic to penetrate into sputum indicates its likely clinical efficacy in chest disease (May, 1968; Zinnemann, 1960). However, available evidence of sputum antibiotic levels is scanty. Furthermore, levels rarely exceed the minimum inhibitory concentration of common respiratory pathogens (May, 1968) and this appears to contradict the undoubted clinical success of several antibiotics in common use for respiratory tract infections. In these circumstances physicians may question the value of sputum assays in their assessment of the patient. However, we believe that the pharmacology of antibiotics varies greatly between individuals and there seems little doubt that those with the ability to distribute an antibiotic into sputum are more likely to show a satisfactory clinical response.

With these points in view we present details of a patient in whom study of serial sputum and concomitant blood levels was made possible by the nature of her condition and accurately predicted the clinical response to a specific antibiotic.

Case report

A 23-year-old married woman attended the Department of Therapeutics at the Royal Infirmary, Edinburgh, because of fibrocystic disease. This diagnosis was established when she was aged 10 on the basis of repeated attacks of abdominal pain, malabsorptive symptoms and almost continuous chest infections. The sweat sodium concentration was 106 mEq/l (normal 0–60). Since the time of diagnosis she had almost continuously expectorated foul green sputum in large volumes and was able to produce specimens virtually on demand. Sputum cultures repeatedly demonstrated *Staphylococcus aureus*, various streptococcal species and *Haemophilus influenzae*. Courses of tetracycline, ampicillin, cloxacillin and erythromycin produced only temporary improvement and we have little doubt that absorption of these antibiotics was impaired. In particular several studies of cloxacillin absorption showed that despite intramuscular therapy of 4 g

daily, the highest sputum assay recorded a cloxacillin level of 3.6 µg/ml, which is considerably below reported *Haemophilus influenzae* inhibitory concentrations (Garrod & O'Grady, 1968).

Encouraging reports of the new lincomycin derivative, clindamycin, suggested activity against all organisms isolated from this patient (Phillips, Fernandes & Warren, 1970; Geddes *et al.*, 1970). Since this drug is also well absorbed (McGehee *et al.*, 1968), it is likely to be of value for treatment of susceptible infections of fibrocystics. An absorption study was therefore performed on our patient, in which serial serum and sputum levels of clindamycin were assayed after her first oral dose of 300 mg. The results of these assays, performed by a standard plate diffusion technique using *Sarcina lutea* as test organism, are shown in Fig. 1 along with serial serum levels of a healthy control subject. It should be noted that the peak serum level of 6.8 µg/ml occurred at 2 hr, significantly later than the control.

FIG. 1. Serial clindamycin levels in blood and sputum after the first oral dose (300 mg).

Sputum clindamycin levels reached a peak of 4.7 µg/ml at the same time, being approximately 69% of the serum level. In general, changes in sputum levels reflected those occurring in the serum.

After several weeks of clindamycin at a dose of 300 mg four times daily the patient's condition has greatly improved and has remained so until the time of writing, 7 weeks later. The sputum is less purulent, the daily volume being reduced to less than 20 ml from over 100 ml.

Discussion

Survival into adult life is rare in patients with fibrocystic disease and the few who do survive are frequently respiratory cripples. The management of respiratory infections in these patients is far from satisfactory although results of continuous long-term cloxacillin therapy are slightly encouraging (Lawson, 1970). The double requisites of reliable absorption and penetration into mucus preclude the use of many antibiotics, otherwise suitable on the basis of *in vitro* sensitivity tests.

The value of clindamycin in our patient was suggested by the known pharmacological properties of the antibiotic, particularly its reliable absorption from the gut (McGehee *et al.*, 1968), and a knowledge of its antimicrobial activity. The absorption study and the clinical response confirmed these theoretical predictions and provided that superinfection with resistant bacteria does not develop it is not unreasonable to conjecture that the initial good response can be maintained.

We agree with the recent suggestion (Zinnemann & Frazer, 1970) that studies of sputum levels of clindamycin are essential before dismissing this antibiotic as a treatment for chronic bronchitis, and indeed such work is currently under way in our unit. The information obtained in our patient should however direct the attention of clinicians and microbiologists to studies in fibrocystic patients with pulmonary infections.

The data presented here may also help to explain previous discrepancies between sputum levels and

clinical results. Many studies of antibiotics in sputum have involved measurement of the average concentration over 24 hr (May, 1968). Thus, periods in which the antibiotic concentration exceeded the minimum inhibitory concentration of the infecting organism might be masked. The rapid variation of clindamycin sputum levels and their close parallel with corresponding serum levels, is well illustrated in Fig. 1. This suggests quicker diffusion of clindamycin than has perhaps been realized and accords quite well with the data recently reported (Mitchell, 1970) concerning 2 hr serum and sputum concentrations of clindamycin in bronchitis.

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