Thorax 1981;**36**:781-783

Serum, saliva, and sputum levels of metronidazole in acute exacerbations of chronic bronchitis

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ABSTRACT We have evaluated the absorption and the penetration of metronidazole into the bronchial secretions and saliva in acute infective exacerbations of chronic bronchitis. Seventeen patients were given 400 mg orally three times daily for seven days and "steady state" levels were measured in serum, saliva, and sputum on the last day of treatment. Mean levels in the three biological fluids were not significantly different. Higher metronidazole levels in sputum tended to occur in patients with higher serum levels. In all but one patient, levels in serum and saliva were well within the therapeutic range. We conclude that this oral regimen results in therapeutic tissue levels in acute exacerbations of chronic bronchitis.

The role of anaerobic bacteria in acute pleuropulmonary infections such as necrotising pneumonia, lung abscess, and empyema is well established, particularly after the aspiration of oropharyngeal secretions.[1 2] However, no attention has been paid to the possible involvement of these agents in acute infective exacerbations of chronic bronchitis. In the course of a prospective investigation into the possible involvement of anaerobes in this very common clinical situation, and the therapeutic implications, we have taken the opportunity to evaluate the absorption of orally administered metronidazole and its penetration into saliva and bronchial secretions.

Methods

Patients admitted to the Luton Chest Unit with acute infective exacerbations of chronic bronchitis were considered for inclusion in this study (full details of the study to be published separately). Briefly, alternate patients acceptable for the study were given metronidazole 400 mg three times daily orally for seven days in addition to their standard treatment of conventional antimicrobial agents, bronchodilators, physiotherapy, and any other necessary therapy. Five ml each of venous blood and 1-5 ml unstimulated saliva and sputum were obtained at the same time from each of the first 17 patients receiving metronidazole on the last day of treatment with this agent. Care was taken to ensure that contamination of saliva and sputum by the most recently taken tablet was avoided. Each blood sample was allowed to clot and serum obtained by centrifugation. The samples of serum, saliva, and sputum were stored at around $-20°C$ until ready for analysis. Sputum samples collected from each patient before the start of antibiotic therapy were likewise retained and comprised control specimens for each patient. The levels of metronidazole and its hydroxylated metabolic derivative 20396 RP were determined in each sample by a specific high pressure liquid chromatography method.[3] The patients comprised 11 men and six women between the ages of 36 and 80 years with a mean age of 61 years and were all known chronic bronchitics attending Luton Chest Clinic on a regular basis.

Results

Individual serum levels ranged from 5·9 to 29·6 μg/ml, sputum levels from 5·0 to 38·0 μg/ml, and saliva levels from 6·6 to 29·6 μg/ml. The mean levels $\pm$ SD in μg/ml of metronidazole and 20396 RP are shown in the table.

The correlation coefficient between saliva and serum levels of metronidazole was 0·36, between sputum and serum levels 0·66, and between sputum

Table *Mean levels of metronidazole and 20396 RP in serum, saliva, and sputum*

	Serum	*Saliva*	*Sputum*
Metronidazole	12·7 $\pm$ 6·1	12·8 $\pm$ 5·8	13·8 $\pm$ 8·5
20396 RP	7·7 $\pm$ 3·2	9·5 $\pm$ 6·7	8·9 $\pm$ 6·1

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and saliva levels 0·38. None was significant at the 5% level.

Discussion

The main finding in this study was that after the oral administration of 400 mg of metronidazole three times daily for seven days, there was no significant difference in mean levels in serum, saliva, and sputum. On this oral regimen, mean serum, saliva, and sputum levels were above the recommended therapeutic level of 6 μg/ml.[4] Therapeutic sputum levels were obtained in all but one patient (sputum level 5 μg/ml), therapeutic serum levels in all but one (serum level 5·9 μg/ml), and therapeutic salivary levels in all patients. There was marked intrapatient and interpatient variation in levels in the three biological fluids. No significant correlation was obtained between levels in saliva and serum or saliva and sputum. Sputum levels were not necessarily reliably monitored by serum levels. However, some discrepancy between serum, salivary, and sputum levels may be attributable to poor co-ordination of clinical specimen collection. Metronidazole is not significantly protein-bound as determined by ultrafiltration methods.[5] It has a pKa value of 2·44 (± 0·035) and this lack of dissociation at a physiological pH of 7·2 suggests that concentrations of the drug in plasma and saliva and any other biological fluid are likely to fall together.[6] It was not always possible to collect all three samples from any one patient at exactly the same time. In 14 of the 17 patients, sputum levels were similar to, or higher than saliva levels, suggesting that levels in expectorated sputum represent true values and not simply salivary contamination of sputum, although some salivary contamination of sputum is to be expected.[7] Particularly in patients with high sputum levels of metronidazole, large volumes of expectorated sputum will result in a considerable loss of metronidazole from the bronchial tree.

The wide range of individual variability and wide range of metronidazole levels in bronchial secretions is comparable with the findings for other antimicrobial agents more frequently used in patients with chronic bronchitis. Such widespread variations have been described using penicillin,[8] ampicillin and amoxycillin,[9–13] tetracyclines,[14–16] and most recently erythromycin.[17] As in the patients treated with erythromycin[17] there was a tendency in the present study for sputum metronidazole levels to increase with serum levels. During acute exacerbations of chronic bronchitis, the bronchial mucosa is the site of infection and local vasodilatation leads to increased vascular permeability and hence to enhanced penetration of antimicrobial agents into inflamed tissue and into bronchial secretions. These agents will reach the bronchial mucosa from the blood along a concentration gradient but sputum levels need not necessarily reflect tissue levels as the dilution factor will depend upon such variables as sputum volume and also leakage of serum through damaged mucosal surfaces into bronchial secretion.

The present study demonstrates that metronidazole levels in serum and sputum after oral administration of 400 mg tds are well within the therapeutic range and we may therefore conclude that tissue levels are adequate.

We are indebted to the nursing staff of the Luton Chest Unit, Mrs G Gottobed and Mrs SR Knight for their assistance, and Dr M Erooga for permission to include patients under his care in this study.

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