COMPARISON OF AMPICILLIN AND TETRACYCLINE IN CHRONIC BRONCHITIS

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Ampicillin (6[D(-)- α -aminophenylacetamido]penicillanic acid; "penbritin"), a new derivative of the penicillin nucleus, 6-aminopenicillanic acid, acts against many Gram-positive and Gram-negative organisms. In particular it has greater activity against *Haemophilus influenzae* than benzylpenicillin. Effective blood levels can be obtained after oral administration (Knudsen *et al.*, 1961). These properties suggest that ampicillin may be valuable in the treatment of chronic bronchitis, and a trial was arranged to compare its efficacy with that of tetracycline.

Material and Methods

The trial took place from November, 1961, to April, 1962. The patients selected suffered from chronic bronchitis, which was defined as "the production of phlegm on most days for at least three months each year" (Fletcher *et al.*, 1959). None of the patients suffered from any other respiratory disease, except for two who had mild bronchiectasis. Patients whose symptoms were predominantly due to asthma were excluded. The dose of both ampicillin and tetracycline was 500 mg. twice daily.

Fifty-nine patients (48 men and 11 women) aged between 24 and 74 agreed to take part in the trial. Four patients did not attend for follow-up for social reasons, two died at home from unknown causes, and one developed carcinoma of the stomach. Of the remaining 52, 22 were given ampicillin during the first three months' treatment followed by tetracycline during the second three months, and 30 were given tetracycline followed by ampicillin. There was no significant difference in the age, sex, smoking habits, or average peak flow of the two groups. The drugs were allocated by random selection; they were prepared in identical capsules, the contents of the capsules being unknown to the physicians and patients. No other antibiotics were given during the trial, but expectorants, bronchodilators, and other treatment which might relieve the patients' symptoms were permitted.

Patients attended monthly and their progress was assessed as follows:

I. At each attendance every patient was asked five questions: (1) Do you feel better, worse, or the same as you did during the previous month? (2) Do you feel more breathless or less breathless? (3) Do you cough up sputum in the morning only or throughout the day? (4) How many days have you spent off work or indoors because of your chest? (5) Have you noticed any side-effects due to the drugs, and, if so, what?

II. At the end of the trial each patient was asked an additional two questions: (1) Has your chest been better, worse, or the same as it was last winter? (2) Did you

feel better during the first or the second three months of the trial?

III. At the beginning and end of the trial and at each monthly visit the following investigations were done: (1) Peak expiratory flow rate (Wright peak flow meter). (2) Examination of sputum.

In order to compare the effect of the two drugs a system of scoring was used. For example, if the patient felt better he scored plus 1, if he felt worse minus 1, and if there was no change 0. Other symptoms were scored in a similar way. Breathlessness was divided into five grades (Fletcher *et al.*, 1959). Sputum quantity was divided into three: nil, occurring first thing in the morning only, and occurring throughout the day. Sputum character was also divided into three: mucoid, mucopurulent, and purulent.

Bacteriology

Each sputum specimen was investigated as follows:

1. The macroscopic appearance was noted.
2. A smear was stained with May-Grunwald-Giemsa stain prior to eosinophil-cell count.
3. The sputum was homogenized by adding an equal volume of 1% pancreatin in buffered saline at pH 7. A blood-agar and a chocolate-agar plate were inoculated with the homogenate using a 3-mm. loop. The blood-agar plate was examined after 24 hours' incubation at 37° C. and the chocolate-agar plate after 48 hours.
4. The remaining homogenate was centrifuged at 1,500 r.p.m. for five minutes and a film made from the deposit. This was stained for eosinophil cells as under No. 2.

5. Preliminary drug-sensitivity screening tests were carried out on all potentially pathogenic organisms using "ditch" blood-agar plates. Where drug resistance appeared to be present the minimal inhibitory concentration (M.I.C.) of ampicillin and tetracycline for the organisms concerned was determined by titration. For *H. influenzae* and *Streptococcus pneumoniae* sensitivity tests, antibiotics were incorporated in heated blood (chocolate) agar, while for all the other organisms nutrient broth was used. Readings of the minimal inhibitory drug concentration were made after 24 hours' incubation at 37° C. With each series of titrations on solid or liquid medium the Oxford staphylococcus was used as the control organism. Apart from noting absolute values for M.I.C., results were expressed as resistance ratios for each organism tested. This figure is the ratio of the M.I.C. of a drug for the strain under test to the M.I.C. of the drug for the Oxford staphylococcus tested under the same conditions. The ranges of ampicillin and tetracycline concentrations used in titrations on those organisms were as follows:

Chocolate agar ($\mu\text{g./ml.}$) 0.01, 0.025 for ampicillin only), 0.05, 0.1, 0.25, 0.5, 1, 2.5, and 5.

Nutrient broth: low resistance in screening tests 0.01–5 $\mu\text{g./ml.}$ as above; high resistance in screening tests—additional concentrations—10, 20, 40, 80, 160, and 320 $\mu\text{g./ml.}$

In the various investigations carried out over the period of the trial it was found that the M.I.C. of ampicillin for the Oxford staphylococcus was 0.05 to 0.1 $\mu\text{g./ml.}$ in either chocolate agar or in nutrient broth. In the case of tetracycline the M.I.C. was 0.25 to 0.5 $\mu\text{g./ml.}$ on chocolate agar and 0.1 to 0.25 $\mu\text{g./ml.}$ in nutrient broth.

Results

Of the 52 patients who took part in the trial 30 (58%) said that they had a better winter than the previous one, 10 (19%) noticed no difference, and 12 (23%) thought they were worse (Table I). The patients who were improved said that they had less cough and sputum, that colds were less likely to develop into an attack of acute bronchitis, and that they had to spend fewer days off work or indoors because of chest trouble. Of these patients, 16 thought that tetracycline was more effective than ampicillin, and 12 that ampicillin was more effective than tetracycline; two were unable to place the drugs in any order of preference.

TABLE I.—Symptomatic Response

Total number of patients in the trial	52
No. of patients whose symptoms improved	30 (58%)
Of patients whose symptoms improved:	
No. who thought ampicillin more effective	12
" " " tetracycline "	16
" " " had no preference "	2
No. of patients whose symptoms were unchanged	10 (19%)
" " " " " worse "	12 (23%)

The "scores" recorded for each drug in the group starting with ampicillin were compared with the scores from the group starting with tetracycline. The scores recorded for ampicillin in both groups were added together and compared with the scores recorded for tetracycline in both groups. There was no significant difference in these results for the two drugs except for those relating to sputum quantity. Ampicillin appeared to be more effective in bringing about reduction of sputum. The mean difference between the scores was 0.22, the standard error being 0.09, which is significant at a level of 5%. The average number of days off work was 8.23 for patients on ampicillin and 8.32 for patients on tetracycline. There was no change in the average peak flow of the two groups.

Table II shows the incidence of *H. influenzae* and *Str. pneumoniae* before the trial and during the first three months. Of the 49 specimens of sputum collected before either drug was given 13 were mucoid. The incidence of *H. influenzae* and *Str. pneumoniae* grown

TABLE II.—Incidence of *H. influenzae* and *Str. pneumoniae* During First Three Months of Trial

	No. of Strains Isolated	No. of Sputa Examined
<i>H. influenzae</i>		
Before treatment with ampicillin	8	20
After 1 month on ampicillin	4	18
" 2 months "	2	14
" 3 " "	4	13
Before treatment with tetracycline	11	29
After 1 month on tetracycline	3	30
" 2 months "	4	23
" 3 " "	3	28
<i>Str. pneumoniae</i>		
Before treatment with ampicillin	3	20
After 1 month on ampicillin	1	18
" 2 months "	2	14
" 3 " "	1	13
Before treatment with tetracycline	3	29
After 1 month on tetracycline	3	30
" 2 months "	0	23
" 3 " "	1	28

from these samples corresponds with that found by May (1954) in single specimens of sputa from chronic bronchitics before chemotherapy. There was a fall in the incidence of *H. influenzae* during the first three months of treatment. Though the figures are too small to attain statistical significance, there appears to be no difference between the incidence of *H. influenzae* in the sputa of patients treated with ampicillin and the sputa of those treated with tetracycline. The incidence of *Str. pneumoniae* is too small for any conclusion to

be drawn from the findings. There was no change in the incidence of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or coliforms.

Ampicillin and tetracycline sensitivity tests did not show an increased incidence of resistant strains of *H. influenzae*, *Str. pneumoniae*, or any of the other organisms isolated during the trial. Of 50 strains of *H. influenzae* isolated, 14 were as sensitive as the Oxford staphylococcus to ampicillin, 5 had resistant ratios (R.R.) of 2, 16 R.R. of 5, 13 R.R. of 10, 1 R.R. of 50, and 1 R.R. of 100. The resistant ratios for tetracycline were: 14 R.R. of 1, 22 R.R. of 2, 13 R.R. of 4, and 1 R.R. of 8. Of 20 strains of *Str. pneumoniae* isolated, all were as sensitive as the Oxford staphylococcus to ampicillin and tetracycline apart from one which had an R.R. of 4 for tetracycline.

Eight patients had sputum with eosinophil counts of 20% or more in two or more specimens. Mulder (1956) described a condition he termed "allergic" bronchitis in which there was a high sputum eosinophil count. Patients with this condition had scanty mucoid sputum which did not contain pathogenic bacteria. Some of these patients never suffered from asthma. In this trial we were unable to find any clinical or other characteristics which distinguished those patients whose sputa showed high eosinophil counts.

Side-effects

Side-effects requiring withdrawal of the drug occurred in five patients on ampicillin and two on tetracycline (Table III). While on ampicillin three patients developed a rash, one palpitations and depression, and one dizziness. While on tetracycline, diarrhoea developed in one patient and indigestion in another. Less serious side-effects occurred in 11 patients on ampicillin and 15 on

TABLE III.—Side-effects

Total No. of patients in the trial	52
No. of patients with side-effects requiring withdrawal of either drug	7 (13%)
No. in whom ampicillin was withdrawn	5
" " " tetracycline "	2
No. of patients with side-effects not requiring withdrawal of either drug	26 (50%)
No. with side-effects not requiring withdrawal of ampicillin	11
No. with side-effects not requiring withdrawal of tetracycline	15

tetracycline. While on ampicillin four patients complained of increased shortness of breath, one of shortness of breath and sore tongue, two of diarrhoea, two of black tongue, one of foul taste, and one of dizziness. While on tetracycline six patients complained of increased shortness of breath, one of increased shortness of breath and palpitations, five of diarrhoea and indigestion, one of foul taste, one of loss of appetite, and one of skin irritation.

Discussion

The value of long-term antibiotics in the management of chronic bronchitis has already been demonstrated (McVay and Sprunt, 1953; Helm *et al.*, 1954, 1956; May and Oswald, 1956; Edwards *et al.*, 1957; Moyes and Kershaw, 1957; Buchanan *et al.*, 1958; Edwards and Fear, 1958; Cherniack *et al.*, 1959; Murdoch *et al.*, 1959; Francis and Spicer, 1960; Dowling *et al.*, 1960; Noach, 1960; Francis *et al.*, 1961). Only one trial failed to demonstrate any noticeable effect (Pridie *et al.*, 1960). These trials suggest that 1 g. of tetracycline daily is an effective dose. A small preliminary trial carried out during the summer of 1961 suggested that an appropriate dose of ampicillin would be 500 mg. twice daily.

The trial has shown that with these doses there is no difference in results obtained with ampicillin and tetracycline in the long-term treatment of chronic bronchitis as judged by symptoms, work record, and bacteriology of the sputum. Side-effects were troublesome with both drugs. *In vitro*, ampicillin has the advantage in being a bactericidal drug, and in high doses might conceivably prove more effective than tetracycline in treating the bacterial complications of chronic bronchitis, especially those due to *H. influenzae*; further work on this point is needed.

Continuous chemotherapy was used to compare ampicillin and tetracycline, for with the limited number of patients available comparison would not have been possible by any other method. Although continuous treatment may be valuable for individual patients in whom infection cannot be controlled by short courses of chemotherapy, there is evidence that the immediate and short-term treatment of an acute exacerbation of infection may be just as effective and should be tried in the first instance (Elmes *et al.*, 1957; Moyes and Kalinowski, 1959; Berry *et al.*, 1960).

Summary and Conclusions

Fifty-two patients with chronic bronchitis were treated alternatively with ampicillin and tetracycline from November, 1961, to April, 1962.

The dose of both drugs was 500 mg. twice daily.

There was no significant difference between the clinical and bacteriological response to the two drugs, except that patients given ampicillin noticed a greater reduction in the quantity of sputum than those given tetracycline.

Sputum cultures showed a decrease in the incidence of *H. influenzae* with both drugs and no significant increase in the incidence of resistant organisms.

Ampicillin is a useful alternative to tetracycline in the long-term treatment of chronic bronchitis.

ADDENDUM.—While this paper was being prepared the results of a trial on the treatment of exacerbations of chronic bronchitis with ampicillin have been published (Ayliffe, G. A. J., and Pride, N. B. (1962). *Brit. med. J.*, 2, 1641). The trial suggested that ampicillin was effective treatment, but it was not possible to show any difference between treatment with ampicillin compared with demethylchlortetracycline or with phenoxymethylpenicillin and streptomycin.

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NIKETHAMIDE FOR SEVERE CO₂ RETENTION IN EXACERBATIONS OF CHRONIC BRONCHITIS

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Inadequate pulmonary ventilation leading to confusion and coma is a familiar and dangerous complication of exacerbations of chronic bronchitis. Once the patient becomes drowsy and fails to cough, secretions accumulate and a further drop in alveolar ventilation may occur. In recent years treatment with tracheostomy, bronchial suction, and artificial ventilation has enabled an increased number of patients to survive the acute episode, but these measures make heavy demands on skilled nursing care. If ventilation and consciousness could be improved by respiratory stimulants treatment would be simpler to administer and less distressing to the patient. Westlake and Campbell (1959) measured the change in arterial carbon-dioxide tension (Pco₂) following intravenous infusions of nikethamide in seven men with acute exacerbations of chronic lung disease. Their results suggested that nikethamide might be of some value; others (Hugh-Jones, 1958) have reported a favourable clinical impression. As this impression of nikethamide is not universally held, the following trial was carried out in two different centres in a further attempt to assess the effects of nikethamide in the treatment of severe carbon-dioxide retention.

Selection of Patients

Our aim was to study patients with chronic bronchitis who had an acute deterioration resulting in severe underventilation and carbon-dioxide retention. These three requirements were defined as follows:

Chronic bronchitis was diagnosed if there was a history of at least three years of chronic cough with expectoration and persistent breathlessness of effort, not

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