PAPERS AND ORIGINALS

Ampicillin Dosage and Use of Prednisolone in Treatment of Pneumonia: Co-operative Controlled Trial*

VALENTINE U. McHARDY, M. E. SCHONELL

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Summary

A controlled trial was carried out to investigate whether the rate of recovery from pneumonia treated with ampicillin is dose related. Sixty-three patients received 1 g ampicillin daily and 63 received 2 g ampicillin daily for seven or 14 days depending on the rate of response. Twenty patients in each of these groups received, in addition, 20 mg prednisolone daily for seven days. The treatment groups were comparable and the results of treatment were similar in the four groups. The only difference which was of statistical significance was that a larger proportion of patients receiving 1 g ampicillin daily became afebrile within one week. All the ampicillin rashes occurred in the patients receiving 2 g ampicillin daily with and without prednisolone. Ampicillin 1 g daily appears to be adequate dosage in the treatment of pneumonia, and the rate of recovery has not been shown to be accelerated by using 2 g. No deleterious effects were noted with additional prednisolone therapy and this appeared to increase the rate at which the patients became afebrile, although the figures were not statistically significant.

Introduction

Ampicillin in a dose of 1 g daily has been shown to be at least as effective as a combination of penicillin and streptomycin in the treatment of pneumonia (Crofton, 1966). The increasing use of ampicillin in both hospital and domiciliary practice led us to investigate whether the rate of recovery from pneumonia might be increased by using a higher dose.

Seriously ill patients with pneumonia are sometimes given corticosteroid therapy, although there is no clear evidence that it is beneficial. We have tried to assess the value of prednisolone by comparing the rate of recovery from pneumonia in patients on ampicillin with and without additional prednisolone therapy.

Patients with a clinical diagnosis of pneumonia admitted to the respiratory wards of the City Hospital, Edinburgh, were included in the trial, which began in January 1966 and was continued until June 1970. The patients were also investigated aetiologically as part of a wider study which has been in progress in the hospital for 10 years. Some of the patients were included in a previous study of pneumococcal typing in pneumonia (Calder *et al.*, 1970).

Patients and Methods

Patients admitted as emergencies to the respiratory wards with a diagnosis of pneumonia were included in this trial. A few were referred from outpatient departments. There were no children under 12 years of age. The criteria for inclusion were radiological evidence of pneumonia or clinical evidence of penumonia if no pretreatment chest radiograph was available. Patients admitted to the trial on clinical grounds alone were subsequently withdrawn if there was no radiological evidence of pneumonia. Patients with pneumonia were excluded if they were either classed as "desperately ill," and judged to be at risk of dying within 24 hours (these patients received a different treatment regimen as part of another trial), or if they were known to be hypersensitive to penicillin or ampicillin. Patients with diabetes mellitus or symptoms of recent peptic ulceration were included in the ampicillin dosage trial but excluded from the random allocation of prednisolone.

* The trial was carried out in the respiratory wards of the City Hospital, Edinburgh (Professor J. W. Crofton, Drs. A. C. Douglas, N. W. Horne, G. J. R. McHardy, D. C. F. Muir). The laboratory work was carried out by Drs. Margaret A. Calder, Margaret Edmond, Sheila M. Stewart, and Helen Zealley at the Wellcome Laboratory, City Hospital, Edinburgh. The trial was co-ordinated by Drs. M. E. Schonell and Valentine U. McHardy, who prepared the report.

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TREATMENT GROUPS

Selection of patients for the trial was made by the physician admitting the patient. Allocation to the treatment groups was made by opening the next of a series of sealed and numbered envelopes containing a card which stated the treatment to be used. Patients were allotted at random to one of the four treatment groups. All were allotted ampicillin in a dose of either 250 mg or 500 mg given by mouth six-hourly for seven days. In some wards the patients were allotted prednisolone at random in a dose of 5 mg six-hourly by mouth for seven days. By protocol the prednisolone was not to be continued more than seven days. If the physician thought the patient's condition was satisfactory at the end of a week ampicillin was discontinued, but if not the same dose was given for a further seven days. Any decision to prolong treatment beyond 14 days was left to the discretion of the physician. The clinician was asked to state his reasons if he gave a second week of treatment, continued treatment beyond two weeks, or changed it at any stage. Treatment was to be changed only if there was clear evidence of clinical deterioration or if organisms isolated were resistant to the drug in use and were thought to be responsible for the pneumonia.

Thus the patients were divided into the following groups: 1, ampicillin 1 g daily; 2, ampicillin 1 g daily plus prednisolone 20 mg daily; 3, ampicillin 2 g daily; and, 4, ampicillin 2 g daily plus prednisolone 20 mg daily.

INVESTIGATIONS

A chest radiograph was obtained as soon as possible after admission and repeated weekly so long as the patient was in hospital. If any residual shadowing was present on discharge the patient was radiographed again about two weeks after discharge and thereafter at intervals of one month until maximum clearing had been achieved. Total and differential white blood cell counts were also done on admission, as was the erythrocyte sedimentation rate (E.S.R.) at one hour for most patients.

Specimens of sputum and laryngeal swabs were sent for culture and sputum was sent for mouse inoculation before treatment was begun in hospital. At the same time blood was taken for culture. Bacteriological examination of sputum was repeated on the second, fifth, and tenth days after admission; if sputum was not available laryngeal swabs were obtained. Sensitivity tests to a range of antibiotics, including the drug in use, were carried out on all potential pathogens isolated by using the disc diffusion method or resistance ratios or both. Complement fixation tests were carried out whenever possible on serum obtained on admission, and at two to three weeks and six to eight weeks after admission. The following antigens were used: influenza A, B, and C; Sendai; parainfluenza 1, 2, and 3; adenovirus; respiratory syncytial virus; psittacosis; *Coxiella* (*Rickettsia*) *burneti*; and *Mycoplasma pneumoniae*.

For purposes of this study only a fourfold rise in titre was accepted as evidence of virus or mycoplasma infection.

PATIENTS STUDIED

A total of 126 patients completed their treatment according to the protocol of this trial. Of these 63 received 1 g ampicillin daily and 63 received 2 g ampicillin daily. In each group of 63 patients, 20 received prednisolone in addition to their ampicillin therapy.

Withdrawals.—If the initial diagnosis of penumonia was not borne out by subsequent investigation the patient was with-

TABLE I—*Comparability of Treatment Groups*

		Ampicillin 1 g				Ampicillin 2 g			
		Alone		With Prednisolone		Alone		With Prednisolone	
		No.	%	No.	%	No.	%	No.	%
	Total patients:	43	100	20	100	43	100	20	100
Sex	Male	19	44	9	45	24	56	9	45
	Female	24	56	11	55	19	44	11	55
Age in years	Average	56·7		64·3		62·0		60·2	
	0-49	13	30	2	10	9	21	4	20
	50-64	12	28	6	30	8	19	4	20
	Over 65	18	42	12	60	26	60	12	60
Previous attacks of pneumonia	None	31	72	10	50	31	72	18	90
	1-2	6	14	7	35	7	16	2	10
	More than 2	2	5	1	5	3	7	0	0
	Not known	4	9	2	10	2	5	0	0
Previous exacerbations of bronchitis	None	24	56	12	60	25	58	14	70
	1-2	1	2	1	5	4	9	2	10
	More than 2	12	28	6	30	12	28	3	15
	Not known	6	14	1	5	2	5	1	5
Prevalence and severity of chronic bronchitis	None	24	56	11	55	26	60	13	65
	Mild or moderate	8	19	5	25	8	19	4	20
	Severe	7	16	4	20	7	16	3	15
	Not known	4	9	0	0	2	5	0	0
Smokers	Now	21	49	11	55	22	51	11	55
	Previously	8	19	3	15	6	14	2	10
	Non-smoker	6	14	4	20	8	19	6	30
	Not known	8	19	2	10	7	16	1	5
Days of illness before admission	0-3	15	35	5	25	10	23	3	15
	4-7	17	40	6	30	19	44	6	30
	8-14	9	21	2	10	9	21	7	35
	Over 14	1	2	7	35	4	9	4	20
	Not known	1	2	0	0	1	2	0	0
Chemotherapy before admission	Yes	17	40	10	50	17	40	13	65
	No	25	58	8	40	24	56	7	35
	Not known	1	2	2	10	2	5	0	0
Severity of illness on admission	Mild	6	14	4	20	9	21	6	30
	Moderate	28	65	14	70	30	70	9	45
	Severe	9	21	2	10	4	9	5	25
Anatomical distribution	Lobar	10	23	4	20	10	23	5	25
	Segmental	10	23	2	10	3	7	1	5
	Lobular localized	14	33	10	50	16	37	10	50
	Lobular diffuse	9	21	4	20	13	30	4	20
	Not known	0	0	0	0	1	2	0	0
Mean initial white cell count (per mm³)		14,100		13,500*		14,000		11,600	
Mean initial E.S.R. (mm at 1 hr)		65 (1 not known)		66 (3 not known)		63 (2 not known)		51 (3 not known)	
Mean peak temperature in first 3 days in °C		37·8		37·5		38·0		37·7	

* Excluding one patient with leukaemia.

TABLE II—*Aetiology of Pneumonia*

		Ampicillin 1 g		Ampicillin 2 g	
		Alone	With Prednisolone	Alone	With Prednisolone
	Total No. of Patients:	43	20	43	20
Significant organisms from sputum or laryngeal swab on admission	Pneumococcus	17	9	20	7
	Staphylococcus pyogenes	3	1	2	4
	Haemolytic streptococcus	1	0	0	0
	Klebsiella pneumoniae	1	0	1	0
	Escherichia coli	0	2	0	0
	Haemophilus influenzae	1	0	1	1
	Pneumococcus and *H. influenzae*	1	1	2	0
	Pneumococcus and *Staph. pyogenes*	3	0	1	0
	No pathogens	16	6	16	8
	Not done	0	1	0	0
Organisms from blood culture on admission	Pneumococcus	4	1	0	1
	Staph. pyogenes	1	0	0	0
	E. coli	0	1	0	0
	Staph. albus (contaminant)	4	2	2	3
Significant virus titres	No. of patients tested	32	15	37	17
	Influenza A	0	1	6	3
	Influenza B	1	0	0	0
	Parainfluenza 1	1	0	0	0
	Adenovirus	0	0	0	1
	Respiratory syncytial virus	1	0	0	0
	Herpes simplex	1	0	0	0
Significant mycoplasma titres	No. of patients tested	34	19	41	18
	Mycoplasma pneumoniae	0	0	1	3

drawn. These withdrawals included cases of cardiac failure, acute exacerbations of bronchitis without radiological changes, bronchial carcinoma, and pulmonary infarction. A few patients with pneumonia who, in error, were not treated according to the protocol were also withdrawn.

Comparability of Treatment Groups.—The four groups were found to be comparable with regard to sex and age distribution and the number of previous attacks of pneumonia or exacerbations of bronchitis (Table I). The patients given ampicillin 2 g daily plus prednisolone (group 4) appeared to have had slightly fewer previous respiratory illnesses. The prevalence of chronic bronchitis and its severity in the opinion of the clinician was similar in these groups. There was no significant difference in the time the patients had been ill before admission to hospital or in the proportion who had received chemotherapy before admission. No significant difference was seen in the degree of leucocytosis or initial E.S.R. on admission or in peak temperature recorded during the first three days in hospital. The classification of severity was made by the physician admitting the case and was based on clinical opinion. Frequency of other chest diseases and other coincident illnesses was similar in the groups, as was anatomical distribution.

Some data on aetiology are given in Table II. There is little difference apart from the fact that more positive blood cultures were obtained in the ampicillin 1 g group (group 1). Serial tests for virus infection were completed in 101 patients, and for infection with *Myco. pneumoniae* in 112 patients. The proportion of positive results is very similar in the four groups, except for an excess of positive titres to influenza A in the groups receiving ampicillin 2 g daily (groups 3 and 4). The few positive titres for *Myco. pneumoniae* were also found in the ampicillin 2 g groups.

Results

Deaths.—Twelve of the 126 patients died. Death occurred in seven patients in group 1; of these three deaths were the direct result of pneumonia and a further three had pneumonia as a contributing factor (together with a myocardial infarction on the second day, cor pulmonale after three months, and left ventricular failure on the fourth day). The seventh patient died from a bronchogenic carcinoma 14 days after admission. One patient in group 2 died as a result of a cerebrovascular accident on the 10th day in hospital. Two patients in group 3 died. One with bronchiectasis and pneumonia died on the 18th day after admission; the other had a myocardial infarction. Death occurred in two further patients in group 4, both the result of pneumonia, but one also had severe chronic bronchitis.

Duration of Treatment.—The total duration of antibiotic therapy received by the patients allotted to the four groups is shown in Table III. It excludes patients in whom treatment was changed and those who died. A slightly higher proportion of those on 2 g ampicillin had at least two weeks of treatment.

Change of Treatment.—The number of patients whose drug regimen was changed during treatment and the reasons for these changes are given in Table IV. None of the 63 patients

TABLE III—*Duration of Regular Treatment*

Duration	Ampicillin 1 g		Ampicillin 2 g	
	Alone	With Prednisolone	Alone	With Prednisolone
< 2 Weeks	14	11	9	8
2 Weeks	10	6	15	1
> 2 Weeks	6	1	6	2
Total patients on regular treatment	30	18	30	11

TABLE IV—*Patients Requiring Change of Treatment*

Reasons for Change	Ampicillin 1 g		Ampicillin 2 g	
	Alone	With Prednisolone	Alone	With Prednisolone
Aetiology or failure of response:				
Pneumococcus	2 (Type 3)	0	1 (Type 18)	0
Staph. pyogenes	2	1	3	4
Kleb. pneumoniae	0	0	2	0
Myco. pneumoniae	0	0	1	0
Myco. pneumoniae and *Staph. pyogenes*	1	0	0	0
No pathogens	0	0	1	0
Toxic effect	0	1*	0	0
Rash	0	0	3	1 (+1)†
Rash, but no further treatment required	0	0	0	2
Other	1‡	0	0	0
Total	6	2	11	7

* Patient with multiple myeloma developed jaundice and pyrexia on fourth day. Not definitely due to ampicillin.
† Patient developed rash but treatment changed for staphylococcal infection.
‡ Cellulitis of wrist.

on 1 g ampicillin developed a rash, whereas a rash occurred in seven (11%) of the 63 receiving 2 g ampicillin, including four on prednisolone.

Resolution of Temperature.—The first day of permanent resolution of temperature was recorded. A comparison of all febrile patients in the ampicillin 1 g groups with those in the ampicillin 2 g groups is shown in Fig. 1. The trend on each hospital day except the second shows the patients in the ampicillin 1 g groups becoming afebrile earlier than those in the ampicillin 2 g groups. This is markedly statistically significant on day 6, $\chi^2 = 7{\cdot}62$ ($0{\cdot}01 > P > 0{\cdot}001$). The same trend was present when patients classed as only mildly ill were omitted. No noticeable difference emerged in the percentage of febrile

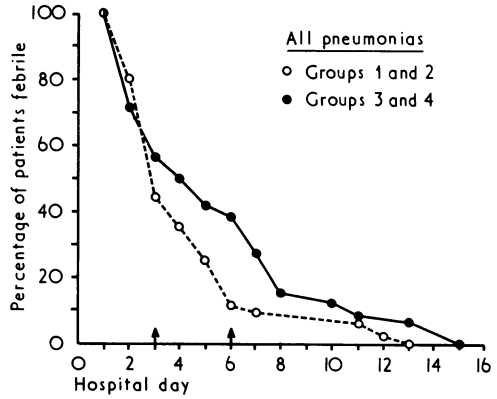

FIG. 1—Resolution of fever in all patients with pneumonia related to dose of ampicillin. Arrows indicate days on which statistical comparisons were made.

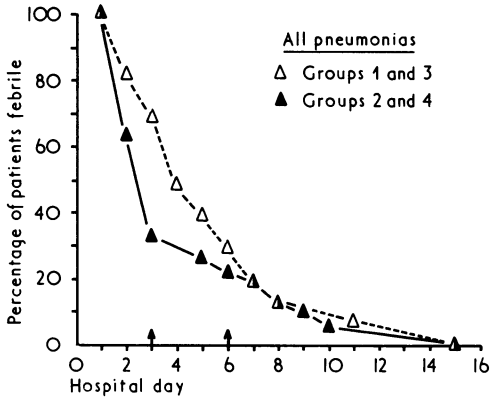

FIG. 3—Resolution of fever in all patients with pneumonia related to treatment with prednisolone. Arrows indicate days on which statistical comparisons were made.

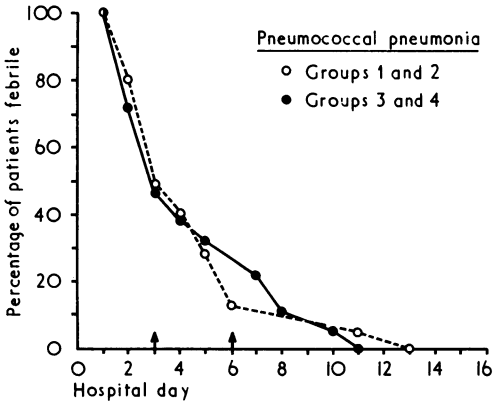

FIG. 2—Resolution of fever in patients with pneumococcal pneumonia, related to dose of ampicillin. Arrows indicate days on which statistical comparisons were made.

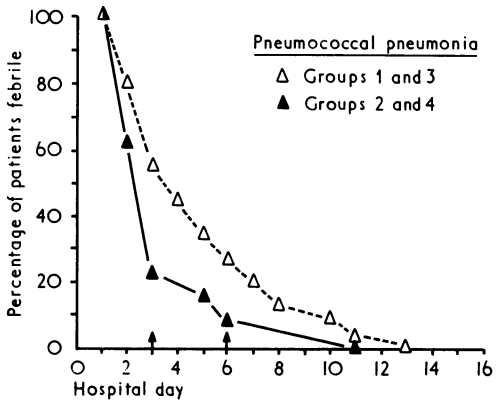

FIG. 4—Resolution of fever in patients with pneumococcal pneumonia related to treatment with prednisolone. Arrows indicate days on which statistical comparisons were made.

TABLE V—*Clearance of Pathogens from Sputum or Laryngeal Swabs*

Day Clearance Achieved	Ampicillin 1 g				Ampicillin 2 g			
	Alone		With Prednisolone		Alone		With Prednisolone	
	No.	%	No.	%	No.	%	No.	%
2nd Day	16	37	9	45	18	42	4	20
5th Day	8	19	2	10	7	16	8	40
10th Day	1	2	1	5	2	5	0	0
After 10th Day	1	2	1	5	0	0	0	0
Not known	1*	2	0	0	0	0	0	0
No pathogen isolated	16	37	7	35	16	37	8	40
Total patients	43	100	20	100	43	100	20	100

* Patient died.

TABLE VI—*Maximum Radiological Clearance*

Time to Maximum Clearance	Ampicillin 1 g				Ampicillin 2 g			
	Alone		With Prednisolone		Alone		With Prednisolone	
	No.	%	No.	%	No.	%	No.	%
0-2 Weeks	17	40	11	55	12	28	9	45
3-4 Weeks	5	12	1	5	7	16	2	10
Within 4 weeks	22	52	12	60	19	44	11	55
5-8 Weeks	6	14	7	35	11	26	3	15
9-12 Weeks	5	12	0	0	6	14	2	10
> 12 Weeks	2	5	0	0	3	7	2	10
Not known	1	2	0	0	2	5	0	0
Deaths	7	16	1	5	2	5	2	10
Total patients	43	100	20	100	43	100	20	100

patients in the ampicillin 1 g groups and ampicillin 2 g groups when febrile patients with only pneumococcal pneumonia were compared (Fig. 2).

Of all febrile pneumonia cases receiving prednisolone (groups 2 and 4) the difference in resolution of temperature between those receiving and not receiving prednisolone did not reach statistical significance on day 3, $\chi^2 = 3{\cdot}72$ ($0{\cdot}10 > P > 0{\cdot}05$) (Fig. 3). The results suggest, however, the possibility of an effect, and the trend is repeated when the mildly ill patients are excluded. Febrile pneumococcal pneumonia patients only are shown in Fig. 4, and again the patients receiving prednisolone (groups 2 and 4) appear to become afebrile more quickly although this is not statistically significant.

Clearance of Initial Pathogens.—The time taken for the organism found in the sputum or laryngeal swab to disappear is shown in Table V. There is no important difference between the groups.

Maximum Radiological Clearing.—The time in which maximum clearing was achieved is shown in Table VI. There is no important difference between the groups.

Discussion

The groups of patients receiving 2 g ampicillin (groups 3 and 4) were slightly more favoured as regards previous respiratory infection and had fewer positive blood cultures. These groups, however, were slightly less favoured in having more accompanying viral and klebsiella infections, which would not be expected to respond to ampicillin therapy. The results in general were if anything less good in the 2 g ampicillin groups. This is shown when comparing the temperature response where the patients in groups 3 and 4 did less well than those in groups 1 and 2, the difference being statistically significant on day 6 (Fig. 1). There was no important difference in the rate of clearance of pathogens from the sputum or of shadowing on the chest *x*-ray film. Of the patients in groups 3 and 4, 11% developed rashes. No rashes developed in the patients in groups 1 and 2. The advantages to the 1 g group, although statistically significant in respect of pyrexia, are unlikely to represent a real superiority to the 2 g dose, but certainly do not support the view that 2 g is better than 1 g. Moreover, all the rashes occurred in the 2 g groups. The higher dose is of course more expensive.

When comparing patients receiving ampicillin and prednisolone with those taking ampicillin alone, patients on prednisolone became afebrile more rapidly (Figs. 3 and 4). This was not found to be statistically significant although it was nearly so. No difference in the rates of clearance of pathogens or of chest *x*-ray appearances was noted. No evidence of deleterious effects was noted in patients receiving the prednisolone.

It is of interest that patients developed ampicillin rashes in spite of taking prednisolone, which might have been expected to dampen the allergic response. However, before concluding that prednisolone should be used as routine treatment in pneumonia it would be wise to carry out a further trial involving a larger number of patients. It should also be remembered that patients with diabetes mellitus or symptoms of recent peptic ulceration were not given prednisolone in this present trial.

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An Assessment of Postoperative Outpatient Cases

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British Medical Journal, 1972, 4, 573–576

Summary

A total of 100 outpatients in the North-East of Scotland were given a simple anaesthetic of propanidid, nitrous oxide, oxygen, and halothane. The study was undertaken to assess what happened to patients when they left hospital after outpatient surgery. An outpatient questionnaire was used, and results show that 31% of patients journeyed home unaccompanied by a responsible person, 73% of car owners drove within 24 hours of the operation, and 9% drove themselves home. Postoperative symptoms of drowsiness (26%), headache (27%), nausea (22%), and dizziness (11%) were recorded, and a higher incidence of symptoms was recorded when surgery exceeded 15 minutes. A new form for outpatient operative procedures in Aberdeen has been devised with modern legal implications in mind.

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Introduction

In British hospitals day surgery is an accepted routine, and as a sequel to the study performed by Fahy and Marshall (1969) it was decided to assess the effects of a simple anaesthetic technique on outpatients in the Aberdeen area undergoing minor surgery. The object was to estimate the anaesthetic postoperative morbidity, and to clarify what happened once these patients left the hospital confines.