PAPERS AND ORIGINALS

Prospective Study of Ampicillin Rash

Report of a Collaborative Study Group*

British Medical Journal, 1973, 1, 7–9

Summary

A multicentre prospective study of 933 patients being treated with ampicillin showed a rash incidence of 7·3%. The rash was commonest in women and patients suffering from viral infections. Most rashes were maculopapular and were not associated with features of true penicillin allergy. We conclude that the development of a maculopapular rash during or after treatment with ampicillin is not in itself a contraindication to future treatment with the penicillins.

Introduction

Shortly after the introduction of ampicillin in 1961 reports began to appear on maculopapular rashes related to its use. The reported incidence of the rash varied from less than 1% to 24% (Willcox, 1963; Geddes and Murdoch, 1964). In a review of the world literature Knudsen (1969) found that 383 out of 13,638 patients treated with ampicillin had developed skin eruptions, an incidence of 2·8%. Pullen and his colleagues (1967) drew attention to the particularly high incidence of ampicillin rash in glandular fever patients, almost 90% developing a rash. A high incidence of ampicillin rash has also been reported in cytomegalovirus mononucleosis (Klemola, 1970) and lymphatic leukaemia (Cameron and Richmond, 1971). The present study was set up to make a detailed investigation of the ampicillin rash and to attempt to explain its pathogenesis. A second object was to investigate any correlation between the incidence of ampicillin rash and protein impurities in the antibiotic by comparing two batches of ampicillin known to differ in their protein content.

True penicillin allergy is a manifestation of hypersensitivity to a number of antigenic determinants of the penicillins or their degradation products. It has been suggested that high molecular weight impurities, both proteins and polymers, may play a part in sensitization and the elicitation of these allergic reactions. On the other hand no firm evidence exists that the maculopapular rash associated with ampicillin has an underlying immunological aetiology. A preliminary study in 1970 compared the incidence of rash with commercially available ampicillin and a preparation from which high molecular weight materials had been removed by charcoal purification of the 6-aminopenicillanic acid (Knudsen *et al.*, 1970). This showed a significant reduction in rash incidence with the purified preparation, although the incidence of rash in both groups was low.

* The collaborative study group was established at the instigation of Beecham Research Laboratories in 1968, in order to investigate the characteristics of the ampicillin rash in a prospective survey.

Beecham Research Laboratories, Chemotherapeutic Research Centre, Betchworth, Surrey

E. A. P. CROYDON, M.B., M.R.C.S., Chief Medical Adviser, Chemotherapeutics
A. W. WHEELER, LI.BIOL., Graduate Biologist
J. J. GRIMSHAW, B.SC., F.I.S., Head of Statistics and Mathmatical Services
WENDY ATKINS, B.SC., Statistics Unit, Graduate Senior Statistician

East Birmingham Hospital, Birmingham 9

M. A. COWAN, M.D., M.R.C.P., Consultant Dermatologist
A. M. GEDDES, M.B., F.R.C.P., Consultant Physician
S. JAIN, M.B., M.R.C.P., Research Registrar
J. G. YASSA, M.B., B.CH., Research Registrar

City Hospital, Edinburgh EH10 5SB

G. W. BEVERIDGE, M.B., F.R.C.P., Consultant Dermatologist
J. A. GRAY, M.B., M.R.C.P., Consultant Physician
J. McC. MURDOCH, M.B., F.R.C.P., Consultant Physician

Seacroft Hospital, Leeds

H. PULLEN, M.B., M.R.C.P., Consultant Physician
N. R. ROWELL, M.D., F.R.C.P., Consultant Dermatologist
J. STEVENSON, M.B., F.R.C.P., Consultant Physician

Subjects and Methods

The trial was conducted over a period of 18 months (from October 1968 to March 1970) in infectious diseases, chest, and urological wards of the Edinburgh City Hospital, Seacroft Hospital, Leeds, and the East Birmingham Hospital.

All patients selected for treatment with oral ampicillin were considered for inclusion in the trial, but strict criteria were laid down for admission. Patients with a history of previous penicillin allergy were excluded, as were those with glandular fever. All trial patients were over the age of 3 years and had white skins. Each patient was observed in hospital for a minimum of nine days after the start of oral ampicillin and was visited daily by the physician co-ordinating the study. If a rash developed this was examined by a dermatologist and a colour photograph was taken. The details of the rash and associated clinical features were recorded in a uniform way.

Relevant bacteriological studies were carried out in all patients. Details were kept of ampicillin dosage, and drugs given simultaneously were also recorded. A full blood count was carried out in all patients on the 1st, 3rd, 7th, and 14th day after the start of treatment and, when practical, samples of serum were

taken for penicillin antibody studies. All patients who developed a rash had blood taken for standard liver function tests, urea, and electrolytes. Antinuclear factor, serum immunoglobulin estimation, and Monospot test for glandular fever were carried out in most cases. Where possible parallel investigations were also performed on non-rash patients.

Only ampicillin made specifically available for the trial was supplied to the wards participating in the study. This was prepared at the beginning of the trial and consisted of two distinct batches. X ampicillin was made from selected 6-aminopenicillanic acid with a known low protein content which was not subjected to any form of purification, but represented the best production material available at the time of the start of the trial in 1968. Y ampicillin was prepared from a batch of 6-aminopenicillanic acid with a higher protein content. Each centre was supplied with X or Y material which was rotated every three months. The clinical staff of the hospital were not aware of the preparation available at any given time. Control procedures were adopted to ensure that the purity of the batches remained about the same throughout the trial period. Injectable ampicillin, which was the commercially available sodium salt of the antibiotic, was sometimes given before oral treatment with X or Y material if the clinical condition of the patient necessitated parenteral therapy.

Results

A total of 933 patients were included in the study; 388 were treated in Birmingham, 277 in Leeds, and 268 in Edinburgh. Of these, 589 were male and 344 were female. Their ages are shown in Table I. Altogether, 434 patients gave a history of previous treatment with penicillin, 182 had a history suggestive of some form of allergy, of whom 32 were allergic to drugs other than penicillin, and 96 gave a family history of atopic diseases.

Of the 933 patients, 707 suffered from infections of the respiratory tract, 54 of which were of proved viral origin. One-hundred-and-fifteen had urinary tract infections, 54 had alimentary tract infections, and 75 had miscellaneous infective conditions. Some patients are included under more than one diagnostic heading. Altogether, 337 patients were treated with varying dosages of injectable ampicillin before starting oral therapy. Over 90% of the patients received drugs other than ampicillin and in a few cases up to six other drugs were taken.

Of the 933 patients entering the trial, 68 developed a rash—an overall incidence of 7·3%. The incidence of rashes in males was 22/589 (3·7%) whereas in females it was 46/344 (13·4%). This difference is statistically significant ($P < 0·01$). The incidence of rashes with X material was 44/519 (5·8%), while with Y material it was 24/414 (8·5%). This difference is not statistically significant. In males the incidence of rashes with X and Y material was similar, but in females there was a significantly lower incidence after treatment with X material (fig. 1). The age and sex distribution of rashes is shown in table I.

FIG. 1—Incidence of rash in patients after treatment with X or Y material (see text).

TABLE I—*Incidence of Rash by Age and Sex*

	Male		Female		Overall	
	Rash	No Rash	Rash	No Rash	Rash (%)	No Rash
3–15 ..	2	15	5	17	7 (17·9)	32
16–30 ..	1	35	1	28	2 (3·1)	63
31–45 ..	1	33	2	35	3 (4·2)	68
46–60 ..	3	166	11	76	14 (5·5)	242
61–70 ..	6	198	10	65	16 (5·7)	263
71+ ..	9	116	16	77	25 (11·5)	193
Age unspecified	—	4	1	—	1	4
Total ..	22	567	46	298	68	865

No correlation was established between a rash and a history of previous penicillin treatment, skin disease, or atopic illness in the patient or his family.

Patients with confirmed viral respiratory tract infections developed a rash more frequently than those with non-viral infections (table II). Patients treated with injectable ampicillin

TABLE II—*Incidence of Rash by Diagnosis*

	Urinary Tract Infection	Alimentary Tract Infection	Non-viral Respiratory Tract Infection	Proved Viral Respiratory Tract Infection	Other
Rash	7	5	42	9	9
No Rash	108	49	611	45	66
Total (% Rash)	115 (6·1)	54 (9·3)	653 (6·6)	54 (16·6)	75 (12)

Rashes in proved viral infections are significantly commoner than all other diagnostic groups ($\chi^2 = 5·46$, $P < 0·05$).

before oral treatment appeared more likely to develop a rash than those receiving oral treatment alone, but this difference fell short of statistical significance. There was no overall relation between the total daily dose of oral amplicillin and the development of a rash, but with X material the rash was dose dependent, most rashes developing in patients receiving 2 g or more daily (table III). In view of the number and diversity of the drugs

TABLE III—*Incidence of Rash due to X Material According to Dosage*

	< 2 g/day	> 2 g/day
Rash	2	22
No Rash	148	242
Total	150	264

prescribed simultaneously, it was difficult to assess their individual contribution to rash incidence. However, none of the drugs taken by patients who developed a rash were exclusively or predominantly confined to this group of patients.

The median time of onset of rash was nine days after the start of oral treatment (fig. 2) and the median duration was six days

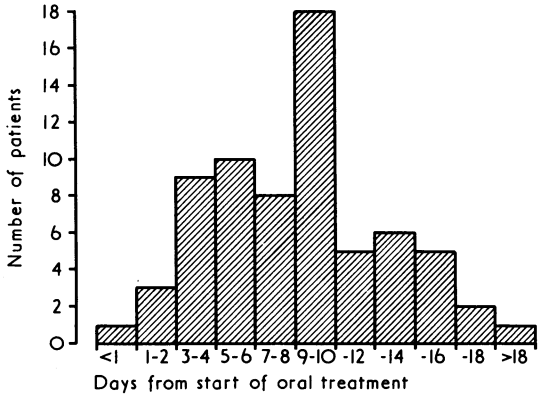

FIG. 2—Time to onset of rash (median = nine days).

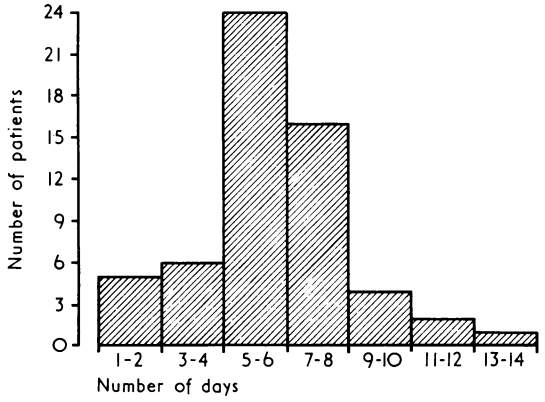

FIG. 3—Rash duration (median = six days).

(fig. 3). The rash usually appeared first on the trunk and spread peripherally to involve most of the body. It was macular or maculopapular in 61 patients, but in only two was it exclusively urticarial. Biopsy of a maculopapular rash showed perivascular and perifollicular aggregates of mononuclear cells, principally lymphocytes, in the dermis. Skin irritation was present in two-thirds of the patients but was generally slight. In most patients the rash was mild and often unnoticed by them, but in a few instances it was more severe with coalescence of lesions, purpura, and slight fever. Mucous membranes were usually not involved. Four had slight swelling of peripheral joints and two had enlargement of superficial lymph nodes. Most patients had completed treatment before the rash appeared, but in 12 treatment was continued in spite of the rash, and in eight of these the rash was fading or had disappeared by the end of treatment. Continuation of treatment was never followed by worsening of symptoms. Diarrhoea and other mild side effects were more frequent in patients who developed a rash.

Haematological studies on rash and control patients showed no significant abnormality specific to rash patients. In particular, eosinophil counts were normal. The biochemical parameters examined were also normal except for transient increases in alkaline phosphatase in some of the rash patients. Estimation of antinuclear factor, serum immunoglobulins, and Monospot test for glandular fever showed no difference between rash and non-rash patients. Examination of sera for penicilloyl-specific antibodies showed no qualitative or quantitative differences between patients with or without a rash.

Discussion

This prospective study has shown an overall incidence of rash with ampicillin of 7·3%. This figure is higher than the average incidence of 2·8% reported in a retrospective review of the literature (Knudsen, 1969). The high figure in the present study can be explained by the careful surveillance of the patients and their observation in hospital for a minimum of nine days.

The aetiology of the ampicillin rash remains obscure. There have been other reports of patients developing rashes during treatment with ampicillin in whom the antibiotic was continued after the appearance of the rash without any adverse effects (Christie, 1964; Pullen *et al.*, 1967). In 12 of the 68 patients in this study the rash was fading or had disappeared by the end of the course of antibiotic and this might suggest a toxic rather than an allergic cause. This theory might be further supported by the fact that patients who develop maculopapular rashes while being treated with ampicillin have been given the antibiotic at a later date without again developing a rash (Christie, 1964; Crow, 1970; Haider, 1971; Bierman *et al.*, 1972).

Ampicillin rashes occur more frequently in patients suffering from viral infections, and an association with infectious mononucleosis and cytomegalovirus infection is now established. In the present study there was a significantly higher incidence in patients with proved viral infections of the respiratory tract. The significance of the relation between ampicillin rash and viral infection is as yet not clear, but if these eruptions are the result of immunological reactions it is possible that they might arise because the virus alters the immunological competence of lymphocytes involved in the reaction.

The noticeable predominance of females in the rash group is so far unexplained, but is confirmed by the results of a similar study in Germany in which the incidence of rash in females was nearly three times that in males (Kroning and Dennig, 1970).

It has previously been suggested that ampicillin rashes are caused by high molecular weight protein impurities which are present in this antibiotic. During immunization experiments in baboons with these impurities, a small number of animals developed eruptions similar to those seen in humans treated with ampicillin (Knudsen *et al.*, 1970). Moreover, these authors showed that purification results in a significant reduction in the incidence of rash in patients. In the present study no specific purification process was involved although two different production batches of ampicillin known to contain different levels of protein were compared. Y material produced a significantly higher incidence of rash in females (fig. 1), but there was no significant difference when both sexes were considered together.

Ampicillin rash is of importance for two reasons. The first is its effect on patients, who may be subjected to discomfort and sometimes to an increased length of stay in hospital. The second point of significance is that many of the patients who have developed ampicillin rashes are labelled as being allergic to the penicillins and may therefore be denied any member of this valuable group of antibiotics in the future.

In this study most of the rashes were maculopapular and only two patients had solely urticarial eruptions, the type usually associated with true penicillin allergy. None of the rashes was accompanied by exfoliation of the skin or significant mucous membrane involvement and there were no anaphylactic reactions. It would clearly be dangerous to classify rashes retrospectively on history alone, particularly as ampicillin, like other penicillins, may rarely cause anaphylaxis or urticaria (Willis and Phair, 1970). In our experience, however, the maculopapular rash which may develop about a week after starting treatment with ampicillin is unrelated to true penicillin allergy, and indeed may not even have an immunological basis. Thus, it is not in itself a contraindication to subsequent treatment with ampicillin or any other penicillin.

We are grateful to those many clinical and laboratory coleagues who contributed to the success of this survey, and particularly to the chief pharmacists of the hospitals involved: Mr. M. G. Spencer, East Birmingham Hospital, Miss R. M. Railton, City Hospital, Edinburgh, and Mr. B. R. Riley and Mr. M. Gaunt, Seacroft Hospital, Leeds.

We are also grateful to Miss Pamela Crabtree for her skilled secretarial help.

References

Bierman, C. W., Pierson, W. E., Zeitz, S. J., Hoffman, L. S., and Van Arsdel, P. P. (1972). *Journal of the American Medical Association*, **220**, 1098.
Cameron, S. J., and Richmond, J. (1971). *Scottish Medical Journal*, **16**, 425.
Christie, A. B. (1964). *Postgraduate Medical Journal*, December Supplement, **40**, 84.
Crow, K. D. (1970). *Transactions of the St. John's Hospital Dermatological Society*, **56**, 35.
Geddes, A. M., and Murdoch, J. McC. (1964). *Postgraduate Medical Journal*, December Supplement, **40**, 81.
Haider, S. A. (1971). *British Medical Journal*, **4**, 364.
Klemola, E. (1970). *Scandinavian Journal of Infectious Diseases*, **2**, 29.
Knudsen, E. T. (1969). *British Medical Journal*, **1**, 846.
Knudsen, E. T., Dewdney, J. M., and Trafford, J. A. P. (1970). *British Medical Journal*, **1**, 469.
Kroning, B., and Dennig, H. (1970). *Arzneimittel-Forschung*, **20**, 1930.
Pullen, H., Wright, N., and Murdoch, J. McC. (1967). *Lancet*, **2**, 1176.
Willcox, R. R. (1963). *British Journal of Venereal Diseases*, **39**, 164.
Willis, R. R. and Phair, J. P. (1970). *Archives of Internal Medicine*, **125**, 312.