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## DRUG RASH WITH AMPICILLIN AND OTHER PENICILLINS

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**Summary** In a comprehensive drug surveillance system which monitored 3985 consecutive medical inpatients, rash attributed to any drug was recorded in 9.5% of 422 patients treated with ampicillin and in 4.5% of 622 patients treated with other penicillins ( $p=0.002$ ). The frequency of rash in 2941 patients not given these drugs was 1.8%. The estimates of attributable risk for ampicillin and other penicillins were thus 7.7% and 2.7% respectively. With ampicillin the route of administration does not appear to affect the risk substantially; with other penicillins there is some evidence that drug rash occurs less frequently after oral than after parenteral administration. The excess frequency with ampicillin is accounted for by a group of patients whose onset of rash is delayed. This suggests that additional antigenic impurities may be present in ampicillin.

### Introduction

AN epidemiological drug-surveillance system, which monitors medical inpatients, has been in progress in three Boston hospitals for periods up to three and a half years,<sup>1-3</sup> and to date almost 4000 consecutive patients have been studied. Trained nurse monitors use standardised forms to record a large amount of data on each patient. The information obtained includes the usual vital statistics, the dates of admission and discharge or death, any history of antecedent allergy, certain routine laboratory data, and a list of the diagnoses made on discharge. Once a patient is admitted to a monitored ward, a record is made of all drugs ordered, together with details of dosage, routes of administration, and starting and stopping dates. Every adverse reaction suspected by the attending physician is noted and promptly investigated. All the information thus obtained is coded and placed on magnetic-tape files, and various computer analyses are then carried out routinely. These analyses are designed to screen a large number of drugs and then to identify any associations between these drugs and designated events.<sup>4</sup> In one such procedure, the frequency of each drug exposure

occurring among patients with a particular drug-attributed adverse event is compared with that of patients who did not experience that particular event.

This screening procedure revealed a striking association between the administration of ampicillin and rash attributed to any drug. Other penicillin preparations were also associated with rash, but the association was less striking.

In a comprehensive review of reports on adverse reactions to penicillin, Idage et al.<sup>5</sup> pointed out that estimates of the frequency of such reactions vary widely, and they stressed the need for further epidemiological research. There is, moreover, evidence to suggest that ampicillin is more particularly allergenic,<sup>6-8</sup> but estimates of frequency are again quite variable.

We have reviewed the surveillance data to assess the frequencies of drug rash with penicillins in general, and with ampicillin in particular.

### Methods

As already indicated, the data for this study have been derived from a routine comprehensive drug-surveillance system. The methods employed have also been described in detail.<sup>1-3</sup> The system records information on rash only when a drug is suspected as the cause, and the nature of such a rash is sometimes unspecified. For the present purpose such reactions will be considered as a group, and collectively referred to as drug rash.

The objectives of this study called for determining the frequency of drug rash for patients who received ampicillin and for patients who received other penicillin preparations. In order to do this it was necessary to list all drug rash attributed to these preparations, patients who received no penicillins, and patients who received other drugs. The total surveillance system was divided into three treatment groups: (1) patients who received ampicillin (the ampicillin group); (2) patients who received other penicillin preparations (the other penicillins group); and (3) patients who received no penicillins (the control group).

The third penicillin group comprised patients who received one or more of the following penicillins:

- Oral: penicillin V, penicillin G, penicillin K, penicillin G potassium, penicillin V potassium, penicillin K potassium.
- Parenteral: penicillin G, penicillin V, penicillin G sodium, penicillin K sodium, penicillin G potassium, penicillin V potassium, penicillin K potassium.
- Oral: penicillin G, penicillin V, penicillin K, penicillin G potassium, penicillin V potassium, penicillin K potassium.

Other penicillins, such as benzathine penicillin or sodium cloxacillin, were not included in the analysis because very few patients received these drugs.

The comparability of the three treatment groups was assessed with respect to the following factors: (1) hospital; (2) age; (3) sex; (4) admission blood-urea nitrogen (BUN); (5) severity of disease, as reflected in survival and length of stay in hospital; and (6) propensity to allergy, as reflected in a previous history of asthma, hay fever, allergic rhinitis, or other manifestation. The frequency distribution in

each of these factors within the three treatment groups were obtained.

Next, the comparability of the ampicillin and the mixed penicillin groups was assessed with respect to the route of administration; and finally, for the ampicillin and mixed penicillin groups, the temporal relationships between the dates of first exposure to each drug and the dates of onset of rash were established. The results are presented graphically for each group separately; only rash occurring within a period from one week before the first day of exposure to four weeks thereafter was considered when the histograms given in the accompanying figure were prepared.

### Results

#### *Patients' Characteristics and Validity of Comparisons*

The average age of the 3985 patients included in these analyses was 59 years, and 48% were males. The numbers of patients in the ampicillin, mixed penicillin, and control groups were 422, 622, and 2941, respectively. The hospitals involved were the Lemuel Shattuck Hospital (L.S.H.) (2000 patients), the Peter Bent Brigham Hospital (P.B.B.H.) (1035 patients), and the Boston City Hospital (B.C.H.) (950 patients).

When the three hospitals were compared, the frequencies of drug rash were closely similar within the mixed penicillin group as well as within the control group. However, in the ampicillin group, while the frequencies of drug rash were similar at two of the hospitals—at 11.6% (L.S.H.) and 9.9% (P.B.B.H.)—at the third (B.C.H.) drug rash was not recorded once in 50 patients who received ampicillin ( $P=0.04$ ) (table 1).

TABLE 1—DISTRIBUTION BY HOSPITALS

| Hospital | Ampicillin group           |               | Mixed penicillin group |               | Control group     |               |
|----------|----------------------------|---------------|------------------------|---------------|-------------------|---------------|
|          | No. of patients            | No. with rash | No. of patients        | No. with rash | No. of patients   | No. with rash |
| L.S.H.   | 190                        | 22 (11.6%)    | 211                    | 10 (4.7%)     | 1599              | 30 (1.9%)     |
| P.B.B.H. | 182                        | 18 (9.9%)     | 183                    | 10 (5.4%)     | 668               | 10 (1.5%)     |
| B.C.H.   | 50                         | 0             | 226                    | 8 (3.5%)      | 674               | 14 (2.1%)     |
| Total    | 422                        | 40 (9.5%)     | 622                    | 28 (4.5%)     | 2941              | 54 (1.8%)     |
|          | $\chi^2=6.3$ ( $P=0.043$ ) |               | $\chi^2=0.9$ n.s.      |               | $\chi^2=0.7$ n.s. |               |

This absence of drug rash with ampicillin could not be accounted for by a tendency to record rash less often at the Boston City Hospital, in view of the frequencies of recorded rash in the mixed penicillin and control groups. The hospital difference in the ampicillin group raised a problem as to whether the type of ampicillin given at the Boston City Hospital differed in its allergenic properties from that given at the other two hospitals (see Discussion). Nevertheless, in order to avoid complicating the analyses, the data from the three hospitals were combined because the relative number of patients in the ampicillin group at the Boston City Hospital was small.

The distributions by age, admission B.U.N., and allergic history were similar among all three groups, and it was felt unnecessary, therefore, to control for them in the analyses. Hospital mortality and length of stay in hospital were closely similar between the mixed penicillin and the control groups. By contrast, in the

TABLE II—DISTRIBUTION BY SEX

| Sex    | Ampicillin group |               | Penicillin group |               | Control group*  |               |
|--------|------------------|---------------|------------------|---------------|-----------------|---------------|
|        | No. of patients  | No. with rash | No. of patients  | No. with rash | No. of patients | No. with rash |
| Male   | 196              | 15 (7.7%)     | 328              | 14 (4.3%)     | 1390            | 19 (1.4%)     |
| Female | 226              | 25 (11.1%)    | 294              | 14 (4.8%)     | 1549            | 35 (2.3%)     |
| Total  | 422              | 40 (9.5%)     | 622              | 28 (4.5%)     | 2939            | 54 (1.8%)     |
|        | $\chi^2=1.05$    |               | $\chi^2=0.01$    |               | $\chi^2=2.76$   |               |

Combined  $\chi^2$  (Mantel-Haenszel) = 3.73 ( $P=0.053$ ).

\* Sex unknown in 2 patients in control group.

ampicillin group mortality was appreciably greater, and the mean duration of stay in hospital was also longer. However, both in the total series of patients and in the ampicillin group, there was no substantial difference in the frequency with which drug rash appeared in patients who died, compared with patients who survived; and there was evidence of a difference in the mean duration of hospital stay in those patients who developed drug rash compared with those who did not. Thus, while it appears that ampicillin was given, as judged by the criteria of hospital mortality and length of stay in hospital, to more severely ill patients, these criteria did not appear to be confounding factors in relation to drug rash, and controlling for them in the analyses was therefore unnecessary. Drug rash also occurred somewhat more frequently in women than in men ( $P=0.05$ ), but it proved unnecessary to control for sex since the sex ratios in the treatment groups were similar (table II).

When the comparability of the treatment groups with respect to the above factors had been established, the ampicillin and mixed penicillin groups were compared with respect to the route of administration (table III). Ampicillin was given only by the parenteral route to 107 patients (25%), only by the oral route to 207 patients (49%), and by both routes to the remaining 108 patients (26%). The corresponding figures for the mixed penicillin group were: parenteral only, 429 (69%); oral only, 51 (10%); and both, 130 (21%). Here, the two treatment groups could not be directly compared, since the frequency of drug rash varied according to the route of administration. Thus, in making comparisons between the mixed penicillin and ampicillin groups, the patients were first divided into subgroups consisting of only oral or only parenteral treatment, and the subgroups were compared separately. The information thus obtained from within the subgroups was then combined by the use of the Mantel-Haenszel procedure.<sup>24</sup> Patients who received both oral and parenteral treatment were excluded from these comparisons because selection factors would have introduced bias into the analyses (see Discussion).

When the frequency distributions of the time of onset of rash in relation to the time of drug exposure were compared, the number of patients with rash in the ampicillin group decreased from 40 (9.5%) to 35 (8.3%), and there was a corresponding drop in the penicillin group from 28 (4.5%) to 24 (3.9%). These reductions resulted from the exclusion of 9 patients in whom rash occurred outside of the stipulated time-limits.

*Frequencies of Drug Rash*

The frequencies of drug rash were 9.5% for the ampicillin group, 4.5% for the mixed-penicillin group, and 1.8% for the control group (table I). The difference between the ampicillin and penicillin groups is statistically significant ( $P=0.002$ ). If the control group

TABLE III—DISTRIBUTION BY ROUTE OF ADMINISTRATION

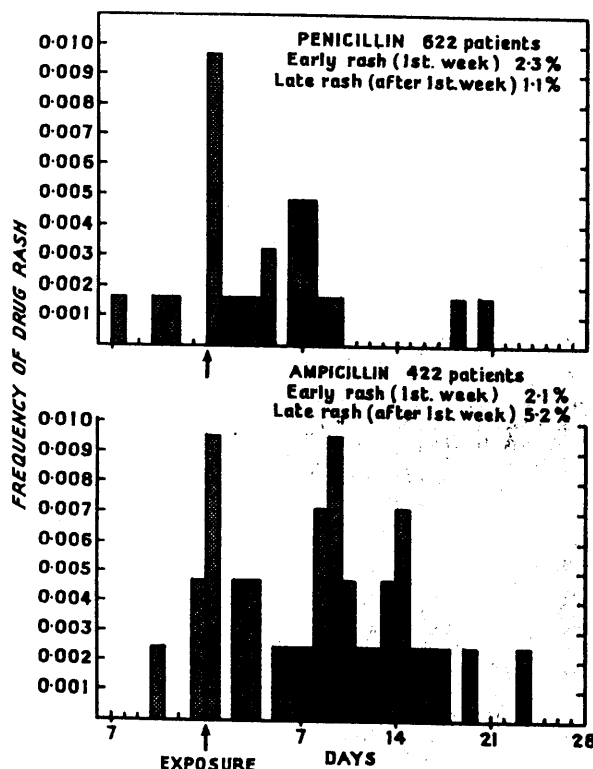
| Route                  | Ampicillin group |               | Penicillin group |               |
|------------------------|------------------|---------------|------------------|---------------|
|                        | No. of patients  | No. with rash | No. of patients  | No. with rash |
| Parenteral .. ..       | 107              | 12 (11.2%)    | 429              | 22 (5.1%)     |
| Oral .. .. .           | 207              | 21 (10.1%)    | 63               | 0             |
| Parenteral and oral .. | 108              | 7 (6.5%)      | 130              | 6 (4.6%)      |
| Total .. .. .          | 422              | 40 (9.5%)     | 622              | 28 (4.5%)     |

Mantel-Haenszel test comparing only parenteral and only oral routes: combined  $\chi^2_1 = 10.78$   $P \approx 0.001$ .

is taken to indicate the background frequency of drug rash, then the estimates of attributable risk in the ampicillin and penicillin groups become 7.7% and 2.7% respectively.

Differences in the frequencies of drug rash between the ampicillin and mixed penicillin groups are still evident when the comparisons between the treatment groups are made, controlling the routes of administration ( $P \approx 0.001$ ) (table III).

Routes of administration were also compared within



Drug rash with ampicillin and other penicillins. The histograms show the distributions of rash according to the number of elapsed days between initial drug exposure and onset. (Frequencies are expressed as the ratio of the number of new cases per day to the total number of patients exposed.)

each treatment group (table III). In the ampicillin group the frequency of rash in patients who received only parenteral treatment (11.2%) was similar to that in patients who received only oral treatment (10.1%); and both of these frequencies were higher than the frequency of rash in patients who received treatment by both routes (6.5%), although the difference is not statistically significant. In the mixed penicillin group, on the other hand, rash was noted in 5.1% of patients who received only parenteral treatment, compared with 0% in patients who received only oral treatment ( $P=0.05$ ). The frequency of rash in patients who received treatment by both routes (4.6%) was similar to that of patients who received only parenteral treatment.

The frequency distributions of times of onset of rash in relation to times of initial drug exposure, in both the mixed penicillin and ampicillin groups, suggested bimodality (see accompanying figure). In each instance there was a group of patients with an early onset of rash subsequent to drug initiation, with a rapid ascent of frequency on the first day. The frequencies of rash occurring during the first week were similar in both groups (mixed penicillin, 2.3%; ampicillin, 2.1%). Late onset of rash began to appear from the beginning of the second week. In the mixed penicillin group the rash tended to occur early in that week, while in the ampicillin group new cases continued to appear up to the end of the third week. The frequency of late rash was greater in the ampicillin group (5.2%) than in the mixed penicillin group (1.1%), and this accounted for the greater overall frequency. Some distortion was present in the data in that, with each successive day after exposure, more patients were discharged from the study. Had they not been discharged, some of them might have developed drug rash. Such distortion was probably slight, and, for comparative purposes, unimportant.

*Discussion*

Ever since the introduction of penicillin in the early 1940s, allergic reactions have been the major problem associated with the use of this drug. The  $\beta$ -lactam amino-penicillanic acid moiety, forming the nucleus, has been implicated as the major antigenic principle; it has been shown that penicilloyl immunoglobulins, or complexed with protein, may account for a substantial proportion of these cases.<sup>1,2</sup> Cross-reactivity between various forms of penicillin has been demonstrated on the basis of animal and human sera.<sup>3,4</sup> The great variation in estimates of the frequency of penicillin allergy arises mostly because of the problems involved in obtaining comprehensive, reliable information.<sup>5</sup> Smith et al.<sup>6</sup> in a carefully controlled, long-term epidemiological study, reported frequency of drug rash attributable to penicillin of 2.8% in a series of 308 patients. A history of previous drug allergy seemed to increase the risk. Unfortunately, the patients in this study were not classified according to the type of penicillin which they received. These workers also stressed the difficulty of determining whether rash was due to penicillin when a patient was also receiving other drugs.

There is now a growing body of evidence suggesting that ampicillin is even more allergenic.<sup>7,8</sup> However, here again, differing methods of data collection and

differing definitions of allergy have resulted in widely varied estimates of frequency.

Pullen et al.,<sup>8</sup> reviewing cases of infectious mononucleosis admitted to one hospital over a five-year period, noted rash in 18 out of 19 patients who received ampicillin. Even if allowance is made for the fact that rash sometimes complicates this disease, and that more severely ill patients may tend both to develop rash more often and to be selected for treatment with ampicillin, such a finding is impressive. In the present series, 9 patients had a diagnosis of infectious mononucleosis; one patient received erythromycin, and none of the others received any antibiotic; drug rash was not recorded in any of these patients.

Anaphylaxis is obviously related to allergy, and is thought to occur in from 0.015 to 0.004% of patients treated with penicillin.<sup>9</sup> Thus far, in the mixed penicillin and the ampicillin surveillance data, there has only been 1 recorded case of anaphylaxis, which occurred shortly after the start of treatment with intravenous aqueous penicillin G. Thus, on the basis of these data, no estimates of the risk of this complication are yet possible, and many more thousands of patients will have to be monitored. However, it is generally accepted that patients who are allergic to penicillin are more likely to develop anaphylaxis when next given the drug, and, if the same holds true for ampicillin, the frequency of this complication may be correspondingly greater.

The present study, by obtaining standardised information on consecutive patients, has determined a background frequency of drug rash; and it has thus been possible to estimate and to compare the attributable risks of drug rash for ampicillin and other penicillin preparations. For ampicillin this risk appears to be substantially greater. Furthermore, the attributable risk may be an underestimate for some ampicillin products: at the Boston City Hospital, where no rash was recorded in the ampicillin group, only one brand of the oral and another brand of the parenteral ampicillin were in use. At the other two hospitals, all four of the brands available in the United States were in use during the period of surveillance. Possibly some brands may be exceptionally allergenic, while others may be comparable in this regard with other penicillin preparations. It must be stressed that the data are only suggestive. A controlled trial would be desirable in determining whether different brands do in fact differ in their proneness to produce drug rash. It has been suggested that different manufacturing processes may result in the presence of impurities in some brands.<sup>20</sup>

With ampicillin, there is no evidence of a difference in allergenicity when oral and parenteral treatment are compared. With the other penicillins it is possible that oral treatment is less prone to produce rash, although this impression is based on small numbers. With ampicillin, the risk of drug rash may be somewhat lower in patients who receive the drug both orally and parenterally than in patients who receive the drug by either route alone. Such a decreased risk would be understandable, since oral and parenteral treatment each produces a considerable amount of rash, and thus the group of patients selected for combined treatment would tend to exclude anyone in whom rash appears

prior to administration of the drug by the second route. The same selective factors would operate far less strongly with the other penicillins. It is for this reason that patients who received treatment by both routes were not included in the comparisons between the two treatment groups when controlling the routes of administration.

Ampicillin is associated with drug rash more often than are other penicillins. Yet, it might be expected, from the molecular structure underlying all of the penicillin preparations, and from the existence of cross-reactivity, that each preparation would tend to produce rash with approximately equal frequency. Furthermore, most of the excess rash with ampicillin seems to occur after an interval of at least a week following exposure, while during the first week rash occurs about as often as with the other penicillins. Late rash with ampicillin also tends to occur over a more protracted period. The following hypothesis is proposed to explain these findings. Firstly, early rash, with both ampicillin and other penicillins, is related to antigens present in all the preparations. This tends to appear in previously sensitised patients, and probably accounts for a majority of those cases with cross-reactivity. Secondly, in the mixed penicillin group late rash reflects allergy occurring for the first time in freshly sensitised patients. With ampicillin, late rash may be due, in some patients, to sensitisation to the same antigens; but the excess, compared with other penicillins, could be due to the presence of additional impurities.

From a clinical point of view, it seems clear that the risk of drug rash, and possibly of anaphylaxis as well, is greater with ampicillin than with any other penicillin preparations. This should be borne in mind before prescribing the drug in preference to other penicillin products.

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