Laboratory Aspects of Erythromycin

Summary: Generally there appears to be a reasonable correlation between the results of laboratory sensitivity tests to erythromycin and the clinical efficacy of the drug in treatment, but relative degrees of resistance are not associated with failure in clinical response in upper and lower respiratory tract disease. The same is possibly true for erythromycin in soft tissue infections due to gram-positive bacteria such as staphylococci and streptococci. Thus erythromycin is a useful alternative to penicillin for example, in tonsillitis, and to ampicillin in lower respiratory tract infections such as bronchitis. Further, it has been used successfully in pre-operative preparation of the colon and there is no evidence that it is liable to encourage resistant organisms in the intestinal tract. On this basis erythromycin must be considered a useful additional antibiotic for use in a local antibiotic policy, since the most important factor in such policies is the availability of a wide selection of agents which allows frequent changes of treatment. Erythromycin appears to be particularly useful for this purpose in general practice where a high proportion of infections has been shown to be due to erythromycin-sensitive bacteria. In addition there are particular indications for erythromycin, e.g. in Mycoplasma infections and chronic lesions such as prostatitis where L-forms (protoplasts) may be involved, and also undoubtedly because it is concentrated in the prostatic secretion.

When erythromycin was introduced over 20 years ago it was regarded as a narrow spectrum antibacterial agent with particular application to the treatment of staphylococcal disease in hospitals. Early experience (3) showed that many strains isolated from lesions became resistant to erythromycin and the experience in a hospital in Edinburgh is shown in Figure 1. After some years of use, the proportion of erythromycin-resistant Staphylococcus pyogenes rapidly increased. It was shown that this change was due to the spread of one predominant phage type of Staphylococcus, presumably selected and propagated under the selection pressure of the antibiotic. This led to the withdrawal of erythromycin for general use and it was reserved mainly for the treatment of streptococcal infection, where penicillin could not be prescribed. In retrospect I consider that bacteriologists and clinicians overreacted to this demonstration of erythromycin resistance which was shown in laboratory sensitivity tests, because the demonstration of such resistance was not correlated with a clinical evaluation of the efficacy of erythromycin in treating staphylococcal disease due to these resistant or sensitive organisms. The situation was that in 1960 only 60% of the strains isolated were sensitive to erythromycin by in vitro tests (Table 1) but as a result of the withdrawal of the drug from general use and the release of selective pressure, by 1974...
Figure 1: Erythromycin-resistant strains isolated each month from lesions (percentage of all strains isolated).

Table 1: Antibiotic sensitivity of Staphylococcus aureus 1960–1974

<table>
<thead>
<tr>
<th>Year</th>
<th>Organisms</th>
<th>Penicillin</th>
<th>Tetracycline</th>
<th>Erythromycin</th>
<th>Cloramphenicol</th>
<th>Kanamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>S. aureus</td>
<td>6</td>
<td>70</td>
<td>60</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>1970</td>
<td>S. aureus</td>
<td>10</td>
<td>86</td>
<td>96</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>1974</td>
<td>S. aureus</td>
<td>16</td>
<td>90</td>
<td>90</td>
<td>100</td>
<td>94</td>
</tr>
</tbody>
</table>

more than 90% of staphylococcal strains isolated in the same clinical areas were sensitive. Thus the value of a restrictive policy in controlling antibiotic resistance was demonstrated.

Laboratory Sensitivity Tests

Sensitivity tests and their results are demanded by many clinicians and undoubtedly in most laboratories much of the work done involves such tests. If they are done they should be carried out carefully and under conditions that are controlled and reproducible, and they should be quantitative. The most commonly used sensitivity test method is the disc diffusion technique and it is possible to make this method quantitative in the routine laboratory (4, 2). Erythromycin is suitable for use in such tests and a linear dose response curve can be produced which is applicable to a wide range of bacterial pathogens (Figure 2). In this way the size of the zone of inhibition of growth can be directly related to the amount of the antibiotic required to inhibit growth (minimum inhibitory concentration).

After these tests have been carried out the interpretation of the results is most important. In most instances the results of laboratory sensitivity tests are related to the antibiotic assay levels found in blood and urine and other body fluids under different schedules of administration. Thus if the inhibitory concentrations of the organism are less than those normally found in the blood the organism can be arbitrarily designated as sensitive, and if the concentration is higher than that obtained in the blood, the organism is said to be resistant. Normally higher concentrations in the urine allow adjustments in these designations so that organisms considered resistant in the tissues may be regarded as sensitive if they are in the urinary tract (Figure 3).

Unfortunately, the models used for both sensitivity tests and assays are relatively simple and even if the conditions of tests are carefully controlled they cannot be said to simulate the conditions in the tissues or body fluids where a wide range of variable factors, some of which inhibit the micro-organism and others which affect the antibiotic, may be found. Accordingly I suggest that the results of individual in vitro sensitivity tests be critically examined and not necessarily taken as an absolute guide to the outcome or treatment with any antibiotic.

The interpretation of the results of sensitivity tests must be related more closely to the results that are obtained in clinical practice and I think it is necessary to examine this problem both from the point of view of the nature of the specimens which are being dealt with in the laboratory and the actual evaluation of the clinical results of treatment.

Antibacterial Spectrum of Erythromycin

Table 2 illustrates the range of bacteria against which erythromycin is active in vitro tests. This is an exceedingly large selection of organisms but it may not mean that erythromycin is active against all the diseases caused by these organisms. In any case, many of these organisms are...