Pharmacoeconomic Studies on Antibiotics
Current Controversies

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It has become more and more evident that not only healthcare administrators but also physicians and nurses must take an active part in trying to reduce costs for healthcare. One field which has received much attention, probably because cost reductions normally do not result in hospital staff reductions, is the cost of drugs.

Pharmacoeconomics has become a special field of interest and scientific efforts. In assessments of economic consequences of drug utilisation, it is important to realise that neither expertise in the field of pharmacology, nor in economic sciences alone suffice; both fields must be combined. If that is not the case, the risk of false conclusions is obvious.

In the area of antibiotics, few high quality studies on pharmacoeconomics have been published, and there are reasons to suspect that quite a few of the publications which have appeared were supported by the pharmaceutical industry. In this article, by an author who has some knowledge in the development and use of antibiotics but who lacks formal training in economic sciences, some problems in evaluations of pharmacoeconomic studies on antibiotics are discussed. For a more extensive overview of the field, the reader should consult a review by Davies and colleagues (1992).

1. Antibiotics as a Pharmaceutical Group

Table I lists some special properties of antibiotics which are relevant for this discussion. The susceptibility of pathogenic bacteria to antibiotics changes over time and also differs between hospital and outpatient environments, between different hospitals, and especially between geographical regions. This should lead to great caution in extrapolating data on an antibiotic from one area or setting to another.

In addition to the properties of antibiotics listed in table I, there have been considerable weaknesses in the way efficacy and safety of antibiotics is documented. Thus, the guidelines used for clinical trials of antibiotics until recently required that a parenteral drug must be used for the entire treatment course (US Food and Drug Administration 1977). In normal clinical practice, injectable antibiotics are used only for a short period in most patients and are followed by oral treatment. In the new guidelines for clinical trials of antibiotics, encouragement is given to the design of trials that evaluate regimens in which a short period of parenteral treatment is followed by oral therapy (Beam et al. 1992, 1993). Moreover, the old guidelines required

<table>
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<tr>
<th>Property</th>
<th>Consequence</th>
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<td>Specific pharmacological activity against bacterial cells</td>
<td>Drug resistance patterns will be decisive for the choice of drug</td>
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<td>Infectious etiology only</td>
<td>Treatment often empirical and includes broad antibacterial spectrum</td>
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<tr>
<td>rarely verified</td>
<td>Therapeutic traditions change rapidly. New and more expensive drugs replace older, less expensive alternatives</td>
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<td>Drug resistance almost</td>
<td></td>
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<td>invariably develops</td>
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that microbiological aetiology should be verified and follow-up samples be obtained in all evaluable patients in a trial, even if the clinical efficacy was a more relevant end-point than microbiological efficacy. The new guidelines recommend trial designs which are far better adapted to normal clinical practice and focus on clinical outcome for most types of infection.

2. Requirements of Pharmacoeconomic Studies on Antibiotics

2.1 Study Design

Due to the rapidly changing resistance situation, retrospective studies or studies using historical controls have very limited value. Pharmacoeconomic studies, for example one by this author (Norrby et al. 1986), have hitherto often been done by taking clinical trials intended for evaluation of efficacy and safety and reanalysing them with a pharmacoeconomic approach. Thus, they were never designed, nor very suitable, for pharmacoeconomic evaluation of treatment regimens.

The optimal study design is to evaluate pharmacoeconomics in prospective, controlled, randomised and, preferably, blinded trials which include evaluation of efficacy and safety. In fact, it should be considered to include pharmacoeconomic analyses as secondary end-points in most phase III trials, and especially in phase IV trials. Since drug costs in clinical practice will be across all patients receiving treatment, exclusions from eligibility should generally not be allowed. An intention-to-treat approach should be used in the evaluation of the results and built into the trial design.

Blinding is important in these trials, since investigator bias may otherwise influence the results. When a double-blind design is not achievable, the study protocol must state which procedures (clinical and laboratory) should be performed and subsequently included in the economic analysis of the results. In open trials, the final evaluation of the patients included should be the responsibility of someone who is blinded as to treatment given (i.e. evaluator blinding).

2.2 Comparability of Treatment Groups

It is essential that treatment groups are comparable in terms of severity and aetiology of infections treated, other underlying diseases, age, etc. This can only be achieved by a randomised trial design. Randomisation should, if the study is not effectively blinded, be performed in a way that excludes the possibility of investigator bias influencing allocation of treatment. This can be done by central randomisation, in which a third party is responsible for randomisation after ascertaining that the patient is identified and found eligible for entry into the study.

Comparability between trial groups can be achieved by prospective stratification, which must be limited to ≤3 strata, or preferably by retrospective stratification in the data analysis. In both cases, all factors to be stratified for must be defined in the trial protocol.

2.3 Route of Administration

In most clinical efficacy and safety trials, antibiotics given by the same route are compared. Normally, a new antibiotic is compared with one which is approved for use in the infection being studied. The outcome in these studies is most commonly that no significant differences can be found in terms of efficacy or safety.

Rarely, these trials include pharmacoeconomic end-points. One reason for that is that the acquisition price of the drug under development is not known. Had price comparisons been done, the new antibiotic would in the majority of trials have been demonstrated to be more costly than the comparator.

The main reason for the higher cost of new drugs is that research and development costs must be retrieved. Thus, one could question whether newer, more expensive antibiotics should be used if they have no proven benefits over existing drugs. It should be noted, however, that this is to a large extent the result of the study design normally used in antibiotic trials, namely one which tends to include only patients with infections caused by or-