Impact of registration procedures on antibiotic policies

B. Schlemmer

Saint-Louis Hospital and University Paris-7, 1 avenue Claude Vellefaux, Paris, France

There is increasing concern over antibiotic resistance and its spread in common bacterial species, such as Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae and Escherichia coli. This results in increased morbidity and mortality. Over consumption of antibiotics has been reported in many settings and underlines the need for improving antibiotic policies. Crude measures of both antibiotic use and antibiotic resistance do not share a strong cause-and-effect relationship. However, this relationship is highly suggestive at a country level, at a hospital level, at a cohort level and at an individual level. In addition to overuse, antibiotic misuse has also to be considered, because of its impact on promoting antibiotic resistance, related to choice, dosage, dosing regimen or duration of therapy [1].

Clin Microbiol Infect 2001: 7 (Supplement 6): 5–8

REGISTRATION PROCEDURES

Registration procedures are now performed, in Europe, at a National and/or European level. Registration is the result of a process which involves pharmaceutical companies as well as regulatory agencies and allows for the assessment of efficacy and safety. During the review process, the risk/benefit profile of the product should be investigated, leading to the granting (or not) of a Marketing Authorization. Accordingly, the Summary of Product Characteristics (SPC) results from an agreement between the pharmaceutical company and the licensing authority and forms the basis for all promotional activities. Taking into account the risk–benefit profile of the product, antibiotic SPCs should inform the future prescriber of all granted indications, product posology, mode of administration, and pharmacodynamics, i.e. the antibacterial spectrum of activity. In this respect antibiotic SPCs allow for the promotion of good antimicrobial practice. The SPC, which is the plain text of the Marketing Authorization and under the responsibility of both industrials and regulators, should be the key to improve antibiotic use because it governs the information given to prescribers. Antibiotic overuse might be controlled by antibiotic restriction, through a clear and definite wording of indications. Antibiotic misuse might be corrected by any information given to ensure appropriate antibiotic use, with respect to dosage, dosing regimens and duration of therapy. The relevance of information to be given to physicians is a specific regulatory issue. It should be based on a critical analysis of data, ensuring proper delineation of indications, adequate dosing and optimal description of intrinsic antibacterial activity as well as relevant information regarding the epidemiology of acquired resistance, if any.

GRANTED INDICATIONS AS A WAY TO SELECT FOR A PROPER USE OF ANTIBiotics

Critical points should be drawn from the data file that has been collected by the company to be given to regulatory authorities. Guidelines regarding the clinical evaluation of new antibacterial agents have been drafted over the last few years by scientific societies (British Society for Antimicrobial Therapy, Infectious Disease Society of America, European Society of Clinical Microbiology and Infectious Diseases) [2] and now form the basis for development or the registration review process. Official guidance was given recently at the European Medicines Evaluation Agency in order to address specific issues pertaining to the clinical assessment of antibacterial drug products [3].

Labelled indications are a key point to control antibiotic use. In outpatients, upper and lower respiratory tract infections are known to account for 75–80% of total antibiotic use. It has been shown that respiratory tract infections with a presumed viral etiology, such as acute bronchitis or rhinosinusitis, are responsible for a large part of unjustified and increasing antibiotic use [4]. Consequently, any information given to prescribers which is able to help select for proper indications and reminders for careful diagnosis before prescribing should be recognized as important tools for good antimicrobial
outpatient practice. On the other hand, at the hospital level, antibiotics are usually used (or overused) for inappropriate surgical antibacterial prophylaxis, or excessive empiric therapy in emergency wards or the intensive care unit.

Clinical trials form the basis for the assessment of efficacy and safety. However, a large experience from clinical trials demonstrates that most of them, in some indications, fail to show any difference in clinical results, even for antibiotics with different antibacterial activities [5]. The reason is that many mild to moderate infections have high spontaneous cure rates, e.g. acute otitis media (AOM) in children over 3 years, sinusitis, acute exacerbation of chronic bronchitis (AECB), and that consequently antibiotics are only partially responsible for the clinical resolution of symptoms.

There is a critical need for clinical trials to select for those patient populations who really need antibiotics, or to look for new endpoints able to differentiate between drugs, rather than only demonstrating ‘equivalence’. This is a crucial issue for upper and lower respiratory tract infections. AOM should be regarded as a different disease in children younger or older than 3 years. Antibiotic therapy should be considered appropriate in cases of purulent AECB that result in an obstructive condition. However, it would not be called for in a large mixed population of smokers with mild to moderate bronchial disease. Pneumonia should be carefully studied with both strictly defined clinical and radiological criteria that patients with only non-specific respiratory signs should be excluded from a pneumonia study.

Whether clinical or bacteriological endpoints should be selected is a frequent matter of controversy. When clinical criteria for efficacy are used, such as in pneumonia, a double-blind design and even an external, investigator-independent assessment are considered critical as a tool for better assessment of efficacy and to compensate for the obvious subjectivity. On the other hand, especially for very specific indications with bacterial eradication as an endpoint, pre- and post-therapy cultures at the site of infection should be performed along with determinations of blood or tissue levels vs dosage. Serial checking of MIC values should be performed when bacteriological failure is detected [5].

Critical trials in carefully selected populations should result in better delineation of indications. Regulators should not only check the studies from a methodological point of view, but in addition should pay increasing attention to patient selection, clinical or bacteriological endpoints and the choice of comparators [6].

The choice of comparators is often problematic. Widely used old agents are no longer considered as valuable if increasing resistance has been described, resulting in an increased risk of poor results. Registered indications for antibacterial drugs have previously been considered as a key issue for the selection of comparators. In addition one should now take into account updated information on antibiotic resistance, MICs for indication-relevant pathogens and the pharmacokinetic profile along with serum or tissue levels.

Finally, SPCs should reflect in their labeling those populations in whom efficacy and, if possible, usefulness, has been demonstrated in a proper way. Criteria for defining those patients should be given to prescribers. Clinical characteristics, or sometimes additional investigations, should aid the physician to select for patients to be treated.

**PHARMACODYNAMIC DATA**

Antibacterial activity forms the basis of antibiotic pharmacodynamics. Guidelines have been given to ensure an accurate evaluation of antibacterial activity, either of intrinsic antibacterial activity or of relevant epidemiological data on acquired resistance [7]. Breakpoints should be established in order to allow for an accurate differentiation between susceptible and non-susceptible strains, using MIC distributions, pharmacokinetic data and clinical results. The prevalence of resistance may vary from one country to another, so physicians should be aware of resistance data in their own country and their consequences regarding the efficiency of empiric antibiotic treatments.

Pharmacokinetic/pharmacodynamic (PK/PD) data have been highlighted as a new way to improve the evaluation of antibacterials. By plotting bacteriological (or clinical) results against antibiotic serum (or sometimes tissue) levels and time, PK/PD data might be useful for a better assessment of efficacy and a justification for optimal dosing regimens [8]. However, tissue level data are very frequently questionable, except from some sites (cerebral spinal fluid), due to methodological and/or technical problems.

In selected, well-designed trials, PK/PD assessment of bacterial eradication would make the evaluation of efficacy more critical. Examples of such trials have been given in acute otitis media, where the bacteriological efficacy endpoint, using the double-tap procedure, has been demonstrated as the key to a more critical assessment of antibiotics, using the concept of ‘in vivo susceptibility testing’ [9]. Differences in intrinsic antibacterial activity or in dosing have been demonstrated and have improved our knowledge regarding the selection of compounds or recommended dosage. The true impact of various MIC levels on clinical results in some bacterial species with moderate antibiotic susceptibility or acquired resistance should be more critically assessed in the future for a better understanding of the therapeutic potential of new drugs.

PK/PD data are of particular interest when trying to define the best dosage and dosing regimens for new compounds [10]. As far as the bacteriological endpoint correctly defines the
outcome in an infectious process, it would serve to assess the
PK/PD relationship of a given drug. However in some
conditions, bacteriological data are questionable, because of an
unclear delineation between colonization and infection, e.g.
AECB, skin and soft tissue infection, or a non-available
bacteriological test of cure. In these situations, clinical data
should be used. However their ability to distinguish one
compound from another or one dosing regimen from another
are different in mild to moderate types of disease and in more
severe conditions. New, more critical clinical endpoints
should be found in some conditions in order to discover any
difference between different drugs or therapeutic regimens. In
this respect, the search for new efficacy markers are of special
interest in the context of AECB, especially with respect to
quality of life or time to the next exacerbation.

Where bacteriological endpoints are not always available,
special attention should be paid to clinical failures in clinical trials.

PK/PD data vs bacterial eradication or clinical outcome
should be considered as the only way to select for optimal
therapeutic regimens regarding antibiotic choice and dosing
regimen, as well as to check for an optimal duration of therapy
[11]. Because the ecological impact of antibiotics has been
clearly related to the overall antibiotic exposure in individuals,
one should select for the shortest possible regimen for a cure
without relapse of the disease.

In an era of increasing bacterial resistance, selecting for more
‘critical’ definitions of dosage and duration of therapy would
serve to improve the ‘microbial safety’ of antibiotics and their
ability to remain active for the future [12]. In this respect some
PK/PD data have been investigated in order to define which
regimens should be considered as the most effective in preventing
the emergence of bacterial resistance during therapy.

**IN VITRO AND ANIMAL MODELS**

*In vitro* models have been developed in order to simulate
human pharmacokinetics and antibiotic behavior against
certain specific pathogens. Various antibiotic levels can be
investigated in order to prepare for the choice or dosing
regimens in phase II-III trials. Future animal models should be
developed in order to obtain a more critical assessment of new
drugs. Human conditions should be simulated with respect to
antibiotic pharmacokinetics and the type of infections, when
possible. Special conditions need to be simulated in order to
assess any role in specialized therapeutic areas when a special
activity is claimed to be effective where older compounds have
failed. In this respect, special models should be included in the
development program of new drugs when aiming at the
treatment of infections due to resistant *S. pneumoniae*,
enterococci, methicillin-resistant *S. aureus* or resistant Gram-
negative bacilli. Investigations of antibiotic combinations
should be performed in such models also. Such experimental
models should not replace clinical trials, but can be useful to
investigate rare medical conditions or antibiotic activity against
unusual pathogens or those with rare mechanisms of resistance.

**ADDITIONAL ISSUES**

Two issues have been raised recently regarding the increasing
concern about old and new antibiotics.

Concerning ‘old’ antibiotics (before 1997 in the European
Community) and their SPCs at the time of arrival of generics,
there is an urgent need for updating and harmonizing SPCs
between European countries. The mutual recognition pro-
dure (MRP) has shown its limitations, especially for old
antibiotics, due to differences between countries regarding the
epidemiology of acquired resistance and the way physicians
usually deal with common infections. In this respect, the lack
of recent clinical efficacy data and updated information on
antibacterial activity and resistance profiles throughout Europe
should be considered as a crucial issue in any attempt to
improve antibiotic use. The lack of relevant product
information actually promotes inappropriate use of antibiotics,
thus there is an urgent need for a reappraisal of antibiotic
classes and the most commonly used antibiotics.

For all antibiotics, old and new, the assessment of efficacy and
safety during registration only resolves some of the key points
involved in the drug evaluation process. There is an increasing
need for the assessment of the place of new and old products in
therapeutic strategies, in order to refine indications, distinguish
between first- and second-line antibiotics, or to identify areas of
additional benefit for selected patients. Post-marketing studies
should be encouraged in order to address specific issues such as
the ‘usefulness’ of antibiotics and the search for the ‘added value’
of recently marketed antibiotic drugs [13].

**CONCLUSIONS**

Improvement in antibiotic policies is the keystone in the
promotion of good antimicrobial practice, either in the
community or within hospitals. However, more accurate
and relevant information on antibiotics is urgently needed. It is
the responsibility of pharmaceutical companies and regulators
to move together towards an improvement in antibiotic
evaluation. This would serve to give prescribers more critical
product information and to help experts create better guide-
lines for antibacterial therapy.

**REFERENCES**

42:125–8


© 2001 Copyright by the European Society of Clinical Microbiology and Infectious Diseases, *CMI*, 7 (Suppl. 6), 5-8