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Concentration controlled and concentration defined clinical trials: do they offer any advantages for antimicrobial chemotherapy?


The rationale for antimicrobial dosing regimens is often difficult to understand, and dosages or dosage intervals are changed or shown to be inappropriate several years after antimicrobials have been marketed (MacGowan et al., 1992; Bauernfeind, 1993; Forrest et al., 1993b; Reeves et al., 1995). For example, twice or three times a day dosing with aminoglycosides has recently given way to once daily therapy with resultant debate about therapeutic monitoring and dosing (Cronberg, 1994; Blaser et al., 1994; MacGowan, 1994; MacGowan & Reeves, 1994; Reeves et al., 1995); recently it has been proposed that the dosage of parenteral ciprofloxacin be increased for pathogens with an MIC > 1 mg/L despite this agent's availability in the UK for 7 years (Bauernfeind, 1993); the dosage of fluconazole in clinical practice is still under debate with evidence of escalation of dosage commonly employed (Working Party Report, 1993; Rex et al., 1994); some agents, such as quinolones and carbapenems, which show concentration-dependent bactericidal activity and significant post-antibiotic effects may be administered once daily but are still administered twice or thrice daily (Gould, Milne & Jason, 1990; Edwards, 1991; Maggiolo et al., 1993); and the dosing regimen for teicoplanin remains controversial with the need for routine monitoring of glycopeptides subject to renewed debate (Freeman, Quintilium & Nightingale, 1993; Wilson, Gruneberg & Neu, 1993; Saunders, 1994; Reeves et al., 1995).

Therefore, there is a considerable need to improve the science of antimicrobial development by acquiring data on clinical responses in relation to in-vivo drug concentrations or dosage so antimicrobials may be used optimally in terms of dosage, dosing interval and method of administration (po, im, iv bolus, iv infusion). This requirement applies to established agents as well as those in pre-marketing development. In short, better understanding of the pharmacodynamics of antimicrobials is required.

The present problems with dosage are related to a number of factors: dosage and dose frequencies are often decided early in the development of a drug when concerns about toxicity may be over emphasised; pharmacodynamic knowledge of the agent or class may have advanced since initial development or since the dosage regimen was proposed; or there may be a poor understanding of the pharmacodynamic factors important in effecting clinical outcome. Aminoglycosides provide a good example of a drug class in which our understanding of dosing has advanced considerably since the introduction of gentamicin (Kovarik, Hoepelman & Verhoef, 1989; Gilbert, 1991), while, in contrast, our knowledge of the critical aspects of dosing with glycopeptides is relatively poor (Reeves et al., 1995). In addition, the amount of data collected to decide on a dosing regimen in phase I studies is generally much greater than that acquired in phase II or phase III studies to optimize dosage or dosing intervals and, for many agents, more or less uniform dosing is used in most clinical trials (Rizk et al., 1992; Pryka & Haig, 1994). Establishing concentration-effect relationships is easier with drugs with linear pharmacokinetics, little person to person variation and limited variations in properties of the pathogen which may effect outcome such as the MIC, MBC, PAE or inoculum effect. This situation rarely occurs in practice even in clinical trials. For example, there is considerable within patient variation in pharmacokinetics, little person to person variation and limited variations in properties of the pathogen which may effect outcome such as the MIC, MBC, PAE or inoculum effect. This situation rarely occurs in practice even in clinical trials. For example, there is considerable within patient variation in pharmacokinetic factors depending whether patients are acutely ill or in the convalescent phase of their illness (Johnson et al., 1990; Cowling et al., 1992). Furthermore, there is often a high degree of variation between patients even if their pharmacokinetics are assessed at the same time in their illness (Cowling et al., 1991; Lovering et al., 1995). These factors have lead to the study of pharmacokinetics in various groups such as the young, elderly, and those with various diseases...
or other co-variables. However, such studies rarely address the effect such changed pharmacokinetics have on clinical outcomes and, usually, relatively small numbers of patients are recruited. In contrast, if the clinical efficiency of two different dosage regimens of an agent are performed then assessment of pharmacokinetics should be mandatory as there may be considerable overlap between serum concentrations in patients receiving different dosages. In this circumstance, measurement of the area-under-the-concentration versus time curve (AUC) probably represents the best assessment of overlap (Eystein-Lønning, 1993). Unfortunately this kind of evaluation is not often performed (Kemper & Kohler, 1992; Carbon et al., 1992), so it is not possible to compare the efficacy of different dosages of the same agent as outcome cannot be related to pharmacokinetic parameters or the degree of overlap in these parameters compared between the dosages employed. Furthermore, even in situations where there is an attempt to link pharmacokinetic parameters to an index of bacterial susceptibility to the therapeutic agent (for example, the MIC) conclusions about which pharmacokinetic parameter is linked to outcome may be confused by the relationship of ‘peak’, ‘trough’ and AUC to each other when fixed dosing intervals are employed (Forrest et al., 1993a,b). In this situation, the data provides information on the total drug exposure required to effect a cure but it does not help determine the optimal ‘shape’ of the serum time curve—for example do we need high peaks or not?

It has been suggested recently, especially when studying drugs with a low therapeutic index that removal of pharmacokinetic variability would benefit clinical trial design. Randomized concentration-controlled clinical trials seek to achieve this objective. In this type of study, patients are given doses of the trial drug which are adjusted to achieve a target concentration or range which is decided before the trial starts. Patients can also be randomized to one of a variety of target concentrations or ranges so concentration response data can be collected (Sanathan & Peck, 1991; Peck, 1993). The performance of concentration-controlled clinical trials could have a number of advantages for investigators, clinicians, the pharmaceutical industry, health care purchasers and, most importantly, patients. One of the reasons for delays in the USA FDA drugs approval process is lack of good concentration or dose efficacy relationship (Lieberman & Nelson, 1993) and this information is likely to be provided by randomized concentration controlled clinical trials. In addition, if pharmacokinetic variability became the main source of variation, the number of patients recruited to clinical efficacy studies could be reduced and a concentration-effect relationship established early in antimicrobial development (Sanathanan et al., 1991). Pharmacokinetic parameters form a more objective measure of drug exposure than drug dose, so our understanding of antimicrobial drug action is likely to increase and a firm foundation for decisions about therapeutic drug monitoring and possible reference ranges for clinical use will be established. Furthermore an automatic check is made on absorption and bioavailability so the quality of antimicrobial formulations can be assessed (Sanathanan et al., 1991; Kelsey, 1987). Finally, and importantly, concentration-controlled clinical trials could be used to explore antimicrobial concentration toxicity relationships and help integrate pharmacokinetic and laboratory parameters of bacterial susceptibility such as MIC, PAE or inoculum effects into clinical efficacy studies. However, it still may be unclear which pharmacodynamic parameter should be controlled unless during pre-clinical development in-vitro or animal models are employed in dose escalation and fractionation experiments to establish this linkage (Blaser et al., 1987; Drusano et al., 1993).

Concentration-controlled clinical trials of antimicrobials would not be without considerable problems. For example, how would the target serum concentrations be decided and which parameter would be controlled: maximum serum concentration (Cmax), trough concentration (Ctrough), steady state concentration, or AUC? It is probable that multiple serum samples would be required from each patient but not as many as in formal pharmacokinetic studies because methods such as maximum a posteriori (MAP)—Bayesian parameter estimation and application of optimal sampling theory (OST) could be employed. MAP—Bayesian analysis is useful when data are sparse or subject to high random error. OST is used to aid collection of data which provide maximum information about the parameters chosen (Forrest et al., 1993a; Levy, Ebling & Forrest, 1994). In addition, control of pharmacokinetic parameters is unlikely to be sufficient as it is the ‘peak’, ‘trough’ or AUC linked to a measure of the pathogens’ antimicrobial susceptibility which determines outcome. This parameter links back...
to data collected in pre-clinical trials. These studies would be difficult to perform in non-hospitalized patients and it is even uncertain whether blood antimicrobial concentrations are suitable surrogates for concentrations at the site of infection. Obviously high quality antimicrobial assays are required which are rapid, specific and accurate as well as able, in some instances, to assay metabolites to help determine whether they contribute to toxicity or efficacy (Shaw et al., 1993). External quality assurance of assay centres will be imperative as will local expert knowledge of drug pharmacokinetics so suitable dose adjustments can be made in order to minimize pharmacokinetic variability in the chosen parameters. All these factors will add considerably to both the cost and complexity of clinical trials for antimicrobials in development and it is unclear who would sponsor similar studies on established antimicrobials.

Perhaps the major theoretical objection to serum concentration-controlled clinical trials is that, for some drugs, the main source of statistical variability is pharmacodynamic rather than pharmacokinetic variation. In infections, pharmacokinetic parameters may vary by up to 50% but for bacterial MICs 100-fold variations are common hence pharmacodynamic variations in combined parameters such as AUC/MIC may be considerable. However, pharmacokinetic and susceptibility parameters can be combined to provide parameters, for example the AUC/MIC or C\text{max}/MIC ratio, which might give a more accurate correlation with clinical outcome than dosage, or simply maintaining concentrations greater than the pathogen MIC (Moore, Leitman & Smith, 1987; Forrest et al., 1993a,b; Körner et al., 1993). A further problem with infection is that, for the most part, optimization of therapy early in the course of infection is crucial and it may take several days in a clinical trial to achieve the desired pharmacodynamic parameter. This is less of a problem with infections requiring longer term therapy such as infective endocarditis, osteomyelitis and AIDs. Indeed it is only in the therapy of HIV infection that concentration-controlled trials have been reported (Flexner et al., 1994). These studies illustrate that concentration-controlled trials can be performed but also that it can be extremely difficult to achieve the chosen target range for the parameter which is selected to control pharmacokinetic variability.

As concentration-controlled clinical trials are likely to be difficult to perform it has been proposed that concentration-defined studies are performed instead. For such trials standard dosages would be given but drug serum concentrations would be measured. At the end of the study patients would be stratified on the basis of pharmacokinetic parameters and relationships between serum concentrations or other parameters and efficacy or toxicity explored (Levy, 1993). This approach has been criticised because of the retrospective nature of the analysis (Peck, 1993) but almost certainly offers a way of collecting useful data on toxicity or efficacy related to concentration.

In conclusion, concentration-defined and perhaps concentration-controlled clinical trials offer an opportunity to provide a more rational approach to dosage, dose frequency and therapeutic monitoring of developmental antimicrobials and form the basis on which to re-assess dosing regimens of older antimicrobials so as to optimise their clinical use in terms of clinical efficacy, toxicity and cost.

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Multiple drug resistant tuberculosis: centralized mycobacterial reference using molecular techniques can help

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The problem of multiple drug resistant strains of tuberculosis, that is strains resistant to at least isoniazid and rifampicin, poses a potential threat to health care services. A number of health care workers in the USA have died from these strains. The fear of fatal tuberculosis in developed countries has been absent for more than a generation, yet if multiple drug resistant strains were to spread through communities the prospect of untreatable tuberculosis could become a reality.

Drug resistant tuberculosis was reported to be increasing in the USA 4 years ago (Snider et al., 1991). Primary isoniazid resistance in the USA was present in 5-3% and secondary resistance in 19-4% of isolates while the figures for rifampicin were 0-6% and 3-2%, respectively.

Several large outbreaks of multiple drug resistant tuberculosis have recently occurred. These differ from previously described outbreaks in that they have spread rapidly and involved larger numbers of hospitalized patients. From 1990 to August 1992 seven hospital outbreaks were reported and affected 7 to 70 people (Dooley & Simone, 1994). The combination of HIV infection and multiple drug resistant organisms is particularly lethal. A recent study from New York indicated that 18-6% of isolates were resistant to isoniazid and rifampicin. The authors concluded that patients should be started initially on at least five drugs to prevent the emergence of further drug resistance (Weltman & Rose, 1994). In the USA factors associated with the likelihood of drug resistant tuberculosis are previous treatment, particularly if prolonged, belonging to an ethnic minority group, particularly from South and South East Asia and Latin America, HIV infection, homelessness or substance abuse (Frieden et al., 1993). Risk factors have yet to be defined in the UK.

In contrast to the experience in the USA, multiple drug resistant strains are as yet rare in the UK. Prospective surveys of tuberculosis notifications have shown primary resistance to isoniazid and rifampicin individually to be between 1-6 and 2-3% in white patients and 4-7 to 13-1% in Asian patients (Medical Research Council Tuberculosis and Chest Diseases Unit, 1980, 1985; Medical Research Council Cardiothoracic Epidemiology Group, 1992). A more recent survey has shown that drug resistant isolates had increased from 8% in 1987 to 15% in 1991 (Warburton et al., 1993). Total notifications for all forms of tuberculosis for England and Wales have also increased by 20% over the same period (Davies, 1993).

The most recent survey, carried out in 1993, has shown that 57% of notifications have occurred in ethnic minority groups: 40% being in those from South Asia (personal communication, J. Watson). Studies from India show primary resistance rates of 14% to isoniazid and secondary resistance of 55% (isoniazid) and 37% (rifampicin) (Trivedy & Desai, 1988). A study from Pakistan has shown 18% resistance to isoniazid (Aziz, Siddiqui & Ishaq, 1989). Recent data from Turkey indicate secondary resistance rates of 36-2% to rifampicin and 30% to isoniazid (Tahaoglu et al., 1994). The problem of increasing resistance is therefore international and with increasing travel could potentially spread (Davies, 1995).

Although blood cultures systems such as the Bactec have been adapted for rapid culture of mycobacteria and can theoretically provide sensitivity results within 7–10 days, in practice this technology is not widely available. This