New quinolones: their role in clinical practice

The starting point for the development of the new family of quinolones — with the recently released products grepafloxacin and levofloxacin shortly to be joined by trovafloxacin, and with others such as moxifloxacin and clinafloxacin in development — was recognition of the shortcomings of the existing preparations. The key question for the new quinolones is how well they address these deficiencies.

INTRODUCTION

The older quinolones, led in the market place by ciprofloxacin, are imperfect antibiotics on a number of counts. Although their meagre activity against anaerobes is seen as being of little immediate clinical concern, it is generally accepted that they exhibit both poor in-vitro and questionable clinical performance against infections caused by Gram-positive organisms, e.g. *Staphylococcus aureus* and *Streptococcus pneumoniae* (Lee et al, 1991). A recently expanding anxiety has been the observed development of resistance that in several settings appears to mirror the volume of quinolone used (Aguiar et al, 1992), while in the background lie worries about the adverse event profiles.

SPECTRUM OF ACTIVITY

There is overwhelming evidence to show that the new quinolones enjoy extended ranges of activity (Ambrose at al, 1997). This is particularly true for Gram-positive cocci, especially the pneumococcus, and includes useful gains against the enterococcus. In addition, despite no clinically meaningful enhancement of potency against *Legionella* species, activity against other atypical respiratory pathogens has improved. Finally some of the newer quinolones, particularly trovafloxacin, demonstrate good activity against anaerobes (Citron and Appleman, 1997). The price of these developments is a loss of potency against some aerobic Gram-negative genera. Concerns in this regard have focused particularly on levofloxacin and pseudomonads, although studies to date have not shown this to be a clinical problem.

PHARMACOKINETICS AND PHARMACODYNAMICS

The newer quinolones show differing developments in pharmacodynamics and pharmacokinetics (Drusano et al, 1998). Led by levofloxacin, they all have improved oral bioavailability over ciprofloxacin. Protein binding is variable and some of the new compounds actually demonstrate increased binding compared to ciprofloxacin, e.g. trovafloxacin.

The newer compounds each have longer serum half lives than ciprofloxacin and this permits once daily dosing schedules. Additionally, the newer quinolones preferentially concentrate in certain tissues, particularly those of the respiratory tract (Piddock et al, 1998). Grepafloxacin administered at a therapeutic dose results in a concentration in alveolar macrophages 5 times that of ciprofloxacin, while the corresponding serum concentration is only one third that of the older antibiotic.

INDUCTION OF RESISTANCE

Although the newer quinolones' mode of action against topoisomerases II and IV is the same as that of their predecessors, it has been suggested that their more balanced mechanism makes these compounds less likely to cause resistance (Baquero et al, 1998). There are some research data supporting this concept, as the newer compounds cause lower resistance mutation rates (Kitzis et al, 1995) than the older quinolones and also show more rapid bacterial killing (Odenholt et al, 1998).

SIDE-EFFECTS AND DRUG INTERACTIONS

There is now some understanding of the relationship between quinolone structure and side-effect risks, e.g. halogen substitution at position 8 in the heterocyclic ring is associated with phototoxicity. Other adverse events, such as QT interval prolongation and seizures, are more of a class event.

There is presently insufficient experience with the newer compounds to indicate whether their adverse event profiles will be different from the older agents, although there is evidence that the modern quinolones are cleaner in terms of drug interactions. Whereas reduced absorption during co-administration with antacids and metallic cations remains a class effect, neither levofloxacin nor trovafloxacin show the theophylline and warfarin interactions found with ciprofloxacin.

CLINICAL STUDIES

Following on from the above, the rub must be whether there are clinical data supporting the preferred use of newer quinolones. Here the issue is bedevilled by investigators invariably undertaking equivalency studies involving a variety — usually the older variety — of established treatments. Projects to date have rarely addressed earlier quinolones and have shown no convincing differences in outcome, however assessed and regardless of the comparator selected.

Most work has been directed towards respiratory tract infections (Garau et al, 1998; Rubinstein et al, 1998) where the enhanced activity of the newer quinolones against pneumococci and atypical pathogens points to potential benefit.

CONCLUSIONS

Despite the current lack of convincing data proving true clinical gain, the promise of the new quinolones is clearly worth pursuing. Good activity against mycobacteria argues that work is needed in this area. The enhanced pharmacokinetic and pharmacodynamic profiles make oral treatment with once daily dosing of diseases such as moderately severe pneumonia, with all that this entails in terms of outpatient management, a real possibility.

The improved spectrum of activity suggests that quinolones might enter the list of monotherapy antibiotics for conditions such as intra-abdominal infection. However, the newer quinolones are not a homogeneous group and the future of their clinical use must include the prospect of separate quinolones having different preferred indications. What is now needed is evidence demonstrating that the promises inherent in the newer quinolones will translate into real patient benefits. HM

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KEY POINTS

- The new quinolones have improved spectra of activity over the older compounds, particularly against anaerobes and respiratory tract pathogens including the pneumococcus.
- The longer half-life of the new quinolones allows the introduction of once daily dosing regimens.
- There are in-vitro but not in-vivo data showing that new quinolones are less inclined than their older counterparts to cause the emergence of resistance to quinolones.
- Drug interactions are less likely to occur with new rather than older quinolones.
- The new quinolones show differences in their features so that separate compounds may have different preferred indications.
- The available clinical trial data dealing with the newer quinolones are limited and many promising avenues of investigation remain to be explored.

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