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Final remarks

Francis A. Waldvogel

Hôpital Cantonal Universitaire, Clinique médicale thérapeutique, 24, rue Micheli-du-Crest, 1211 Genève 4, Switzerland

Some new and important concepts have emerged from the research of the last five years about quinolones in general and pefloxacin, in particular. These can be summarized as follows.

Microbiological aspects

The quinolones in general, and pefloxacin in particular, have minimal bactericidal concentrations (MBC) that are close to their minimal inhibitory concentrations (MIC). They all exert a strong postantibiotic effect, are active to some extent on resting bacteria and show a paradoxical decrease in activity if used at very high concentrations, or in the presence of protein inhibitors. Development of resistance has become well documented, mostly in *Staphylococcus aureus* and *Pseudomonas aeruginosa*, less often in other bacteria such as the Enterobacteriaceae. The development of resistance in *S. aureus* and *P. aeruginosa* is of some concern when quinolones are used for the long-standing treatment of osteomyelitis, and of lung infections in patients with cystic fibrosis.

Biological properties

Subinhibitory concentrations of pefloxacin have been shown to decrease the adherence of Gram-negative bacteria to intestinal cells, and of Gram-positive bacteria (*S. aureus*) to buccal cells. A decrease in adherence after treatment with sub-MIC concentrations has also been demonstrated with *Escherichia coli* on uroepithelial cells, and with *Enterococcus faecalis* to a platelet fibrin matrix. Uptake of pefloxacin, with higher intracellular than extracellular concentrations at 120 min (ratio up to 8) has been shown for macrophages, polymorphonuclear leucocytes and fibroblasts. Pefloxacin seems to concentrate in the cytoplasm. Release of pefloxacin with outward movement from the cell also occurs, and is influenced by the degree of activation of the macrophage; the intracellular concentration of pefloxacin therefore depends on these two mechanisms: penetration and extrusion.

Pharmacology and toxicology

In order to ensure safety, although the maximum tolerated plasma concentrations have not been clearly defined, the dosage of all quinolones should be reduced in renal failure

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(creatinine clearance below 10 ml/min) with doubling of the interval between doses except in the case of pefloxacin. All the quinolones are poorly removed by haemodialysis, and therefore no change in the regimen is required under such conditions. Liver failure also influences the pharmacokinetics of the quinolones, but most of the pharmacokinetic data have been obtained in cirrhotic patients, who unfortunately are not equivalent to patients with impaired hepatocellular or hepatosecretory functions.

Review of the clinical studies has shown a 2·3–3·8% incidence of side effects. Of greatest clinical importance are certainly the effects on the central nervous system, which were found in 0·9% of patients. One of these side effects has been quite well delineated, and involves convulsions under well-defined clinical or experimental conditions.

Thus, fenbufen and enoxacin given together have led occasionally to seizures in man, whereas fenbufen and any quinolone may lead to convulsions in animals. Other side effects of minor importance to be considered are arthralgia, and thrombocytopenia; the latter has occurred in association with heparin treatment, and it is still difficult to define which of the two drugs is the major culprit in inducing this effect.

Clinical aspects

Some important new clinical successes have to be stressed. Encouraging results are now being reported with pefloxacin in the long term treatment of chronic osteomyelitis, although most of the cases reported also involved concomitant surgery. In typhoid fever, a 7-day course of pefloxacin seems to be highly efficacious. Interesting results have been obtained with pefloxacin in bacteraemia and meningitis, with a loading dose of 800 mg. Since reported side effects have so far been neither dose- nor time-related, this high dosage seems to deserve further investigation as an effective means to treat life-threatening infections. Interesting results have also been obtained with pefloxacin, either as single therapy or in combination therapy, in pulmonary infections by *Legionella* spp. Single-dose pefloxacin administered in lower urinary tract infections seems to give in the long run fewer recurrences than treatment with a single dose of a β-lactam antibiotic, possibly because of the longer half-life and/or the postantibiotic effect of the quinolone.

The future

Although the last years of investigation have helped to define better many features of pefloxacin therapy, several aspects of quinolone treatment deserve further investigations. Non-absorbable quinolones, which would be used only for gastrointestinal decontamination (neutropenic patients, intensive care unit patients), would be an interesting adjunct to our present armamentarium. Increased activity against streptococci, *S. aureus*, and other Gram-positive bacteria, is being achieved now with some of the newer quinolones such as temafloxacin and sparfloxacin . These studies deserve further development. Compounds with a narrow spectrum, but increased activity against anaerobes, would be of help in gastrointestinal infections. A better understanding of the non-antimicrobial effects of the quinolones (effects on adherence, phagocyte interaction, intracellular penetration) may help to define better

their usage as prophylactic and therapeutic agents. The possibility of administering high dosages of pefloxacin in indications such as bacteraemia and meningitis has to be further investigated in detail. The investigations that we are able to review at the present time may represent only the beginning of the therapeutic potential of the quinolones.