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Quinolones in the Aged

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Abstract

Pharmacokinetic studies of fluoroquinolone antibacterials generally demonstrate some quantitative alterations in elderly compared with younger populations. The most common observations are an increased maximal plasma drug concentration and area under the concentration-time curve, which are primarily attributable to the 10 to 15% decrease in lean body mass in the elderly.

For quinolones excreted primarily by the renal route, there is a prolongation in elimination half-life correlated with the aging-associated decline in creatinine clearance. Quinolones with major routes of nonrenal clearance will not usually show a prolongation in half-life because of compensatory relative increases in nonrenal mechanisms. Alterations directly attributable to aging alone, however, are minor, and vary between different quinolones. They do not justify a consistent need for dosage alterations on the basis of age alone. Agents with primarily renal excretion, such as ofloxacin or levofloxacin, may require dosage adjustment in the very elderly or the frail elderly, if significant decreases in creatinine clearance are present.

No age-related differences in adverse effects of fluoroquinolones have been reported. Studies in both community-dwelling and institutionalised elderly populations have consistently shown quinolones to be as effective as comparative parenteral or oral therapy. While elderly populations may be at greater risk of adverse effects because of comorbidities and concurrent therapies, an increased occurrence of adverse events in elderly populations receiving quinolone antimicrobials relative to younger populations has not been reported.

Several issues are relevant to a consideration of fluoroquinolone antimicrobial use in elderly individuals. Firstly, the pharmacokinetics in this population may be altered by aging-associated physiological changes, necessitating alteration in dosage or dosing frequency. Associated comorbidities such as renal or hepatic impairment or congestive heart failure may also impact on drug disposition. Adverse drug effects could possibly occur more frequently for the same reasons, as well as because of drug interactions with other medications prescribed for many elderly people. Finally, there is the issue of clinical efficacy in elderly populations and whether it is equivalent to that in younger populations.

1. Pharmacokinetics of Quinolones in the Elderly

Several physiological changes occur with normal aging which may alter pharmacokinetic parameters in elderly individuals.[1-3] Examples of these changes include reduced gastric acidity, which could decrease absorption of agents which require an acidic environment for absorption, or increase absorption for those degraded by gastric acidity. There is also a general reduction in intestinal motility in the elderly, which prolongs the time period for absorption, but may also result in a slower time to maximal plasma drug concentrations (C_{max}) after oral therapy. In addition, the absorptive surface of the gut is decreased, which may decrease bioavailability. Serum albumin is decreased in the elderly, and this may alter plasma concentrations of highly protein bound agents.

A consistent decrease in lean body mass with aging, which averages 10 to 15%, and the concomitant decrease in body water to fat ratio, will decrease the volume of distribution of water soluble agents in elderly compared with younger individuals. There is a variable, but consistent aging-associated decline in renal function, which averages a 40% decline in creatinine clearance between middle and very old age (>80 years). This will delay excretion and prolong the elimination half-life ($t_{½\beta}$) for agents which are excreted primarily through the urine. There is also a decrease in hepatic metabolism with aging, but the extent is not well characterised and the impact on drug disposition not clearly defined.

Despite all these age-related changes and their

potential impact on pharmacokinetics, they are not of sufficient magnitude or consistency that quinolone dosage alteration solely on the basis of age is routinely recommended. Where dose modifications are appropriate, they are mandated by lean body mass and creatinine clearance, rather than age *per se*.

In general, where pharmacokinetic changes are observed for quinolone antimicrobials in elderly compared with young populations, there is an increased C_{max} and increased area under the plasma concentration-time curve (AUC).[4-10] The decrease in lean body mass in the elderly is assumed to explain these observations. In addition, decreased renal clearance of these drugs is usually observed, which is fully explained by the aging-associated decline in renal function.[7,9,10] For agents primarily excreted through the kidneys, such as ofloxacin and levofloxacin, this may lead to a prolongation in the elimination half-life.[10,11] The majority of quinolones also have nonrenal clearance mechanisms, including metabolism and transintestinal excretion.[5,6] There is usually no substantial increase in $t_{½\beta}$ of these agents in the elderly, as the nonrenal clearance mechanisms compensate for the decline in renal clearance. Other pharmacokinetic parameters, such as absorption and metabolism, have not been shown to differ between elderly and younger populations.[4]

For those quinolones with primarily renal excretion, the increase in $t_{½\beta}$ with decrease in creatinine clearance may be of sufficient magnitude in the very aged or frail elderly that some adjustments in dosage levels should be considered routinely in such patients. Ofloxacin and levofloxacin are the agents of greatest concern.[10,11] Repeated administration of these agents leads to accumulation in the very elderly. Other agents such as enoxacin and lomefloxacin which also have substantial renal clearance also show some accumulation with repeated dosing, but to a lesser extent.[12] If dosage was routinely based on lean body mass and renal function, there would be no need for an age-associated adjustment.[11] However, in most cases, creatinine clearance is not available at the time of prescribing. Thus, it is more practical to recommend dosage adjustment for selected elderly individuals in whom low creatinine clearance values are anticipated. Patients over 80 years of age and the extremely frail elderly with a marked decrease in lean body mass are those for whom this dosage adjustment should be considered. For ofloxacin, it is suggested that the usual dose of 200 to 400mg twice a day is adjusted to 200 to 400mg once a day in such patients.[10,13] Studies document that ofloxacin 200mg once a day is effective in elderly populations with urinary infection.[13] While dosage adjustment for other fluoroquinolones such as fleroxacin or lomefloxacin has been suggested for the very elderly, it is not generally practised.[6]

The newer quinolone antimicrobials, sparfloxacin,[14] grepafloxacin,[15] trovafloxacin[16] and moxifloxacin[17] are primarily excreted by nonrenal mechanisms and do not demonstrate pharmacokinetic alterations with age. Clinafloxacin and gatifloxacin are, however, excreted primarily by the urinary tract. These agents may have a prolonged half-life in the elderly, but whether this necessitates dosage adjustment is not yet determined. Obviously, alteration in dosage according to creatinine clearance is always necessary in drugs excreted primarily by the renal route.

2. Adverse Effects

Since the initial introduction of norfloxacin and ciprofloxacin, the quinolone antimicrobials have been used widely in elderly populations for many clinical indications. Nevertheless, there has been little systematic study of potential differences in adverse events in elderly compared with younger populations.

Objective observations are those primarily reported in clinical trials and post-marketing surveillance. Clinical studies of quinolone use in the elderly have enrolled patients with urinary tract, respiratory tract, skin and soft tissue and joint infections and those receiving surgical prophylaxis, and have not noted an increased occurrence of adverse effects compared with younger populations.[13,18,19] Studies have not, however, directly compared elderly with younger populations with respect to efficacy or outcomes. In addition, elderly patients with multiple comorbidities and receiving multiple medications would be excluded from enrolment in most clinical trials.

The more serious and limiting adverse effects of fluoroquinolone antimicrobials, including the temafloxacin syndrome, phototoxicity, neurotoxicity and arthropathy have not been reported to occur with increased frequency in elderly compared with non-elderly populations.[20] However, prospective or case control studies, which might define the precise risk, have not been published. Thus, it is possible an age-association could exist but has not been appropriately studied.

One report of post-marketing surveillance for adverse drug effects from Japan suggested that, for ofloxacin, there may have been an increased occurrence of reported adverse reactions with age that was not observed with ciprofloxacin.[21] This report does not provide specific information regarding the adverse effects noted. The association with ofloxacin, however, would seem consistent with increased accumulation of this agent with declining renal function, given that it is excreted almost entirely by the renal route.

Overall, however, available reports and experience do not suggest a clinically significant excess risk of toxicity in elderly populations with fluoroquinolone use. Despite the lack of systematic study of this issue, the frequent use of fluoroquinolones in elderly populations, including the highly impaired institutionalised elderly, means that substantially aberrant trends in toxicities compared to younger, healthier, populations should have been noted.

One particular concern for the elderly population is the potential impact of quinolone therapy on cognitive function in the confused or mildly demented elderly. There are anecdotal reports from practitioners describing increased behavioural and cognitive problems with quinolone therapy in elderly patients. This problem, however, has been directly addressed only occasionally in appropriate clinical studies. In one study, McCue et al.[13] measured activities of daily living, psychobehavioural scale and mental status in individuals treated with ofloxacin or ciprofloxacin for asymptomatic or symptomatic urinary infection. Measurements were obtained immediately prior to treatment, at days 2 and 3 of treatment, at 5 to 9 days and 4 to 6 weeks post-treatment. The question asked in this study was whether there was a significant decline in these parameters associated with urinary infection. However, the measurements would also provide insight into whether quinolone therapy leads to decline in function, although an end of therapy assessment was not made. No differences were observed in functional or mental status with any of these parameters with either quinolone. In another study of ofloxacin therapy,[19] no evidence of deterioration in mental or functional status was observed with ofloxacin therapy when used to treat urinary infection, pneumonia or skin infection. These studies suggest that if such problems occur, they are idiosyncratic rather than a consistent observation. This is an area where further studies should be conducted.

3. Conclusions

Fluoroquinolone antimicrobials are widely used in elderly populations. For some quinolones consistent pharmacokinetic changes are observed in the elderly, including an increase in C_{max} and AUC of these drugs. These changes primarily reflect aging-associated decline in lean body mass and decreased tissue distribution. Quinolones excreted primarily by the kidneys may also have a prolonged elimination half-life, because of the age-related decline in creatinine clearance. These changes are not of such consistency or magnitude that alteration in dosage regimen is recommended on the basis of age alone. However, with agents with primarily urinary excretion, dosage adjustment in the very old or frail elderly populations may be considered because of the anticipated decreased creatinine clearance.

There is no evidence of increased adverse effects with use of fluoroquinolones in elderly compared with younger populations. Experience is still limited with the more broad spectrum agents recently introduced which have primarily nonrenal clearance mechanisms, and further observations with these agents is needed. Based on the information available, however, fluoroquinolone antimicrobials are well tolerated and effective therapy in elderly populations. In fact, observations based on their widespread clinical usage to date are consistent with a remarkably good tolerability of these agents in this population.

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