

Prescribing Patterns and Rational Use of Specific Antibiotics in the Elderly-Review

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ABSTRACT

The antibiotic therapy in the geriatric population requires a more comprehensive and cautious approach because of the increased susceptibility of the elderly to the adverse effects. This is possible by restricting their usage for infections that are not complicated and by acquiring a thorough knowledge on the pharmacokinetics and pharmacodynamics of these drugs. The role of therapeutic drug monitoring is also vital in ensuring the safety and efficacy of the antibiotic use in this population.

KEYWORDS:

Antibiotics, Pharmacokinetics, Pharmacodynamics, Polypharmacy, Elderly

I. INTRODUCTION

Antibiotics are one of the most frequently prescribed drug classes in the geriatrics. This trend is further accelerated by the susceptibility of the elderly to various infections. The changes in the pharmacokinetic and pharmacodynamic factors also make the need for optimal management of the antibiotic therapy very crucial. The presence of polypharmacy can pose a major threat in maintaining the appropriateness of the antibiotic prescriptions in this population. The objective of this review is to discuss the prescribing pattern and considerations for the rational use of the antibiotics in the geriatric population.

II. PHARMACODYNAMICS AND PHARMACOKINETICS OF ANTIBIOTICS IN THE ELDERLY

In elderly patients, pathophysiological changes may affect the pharmacokinetics and pharmacodynamics of antibiotics.

Body composition changes can affect the pharmacokinetics. There is a substantial influence in the pharmacokinetics of administered drugs in elderly patients by malnutrition and sarcopenia. Drug distribution can be affected by reduced fat tissue and lean body

mass. Accumulation of lipophilic drugs are reduced by the reduction in the mass of adipose tissue. Also the distribution of hydrophilic drugs can be affected by the changes in muscle mass and redistributed body water effect. This could lead to greater fluctuations in drug plasma concentrations. In cachexia patients, the drug metabolism can be reduced by malnutrition which has been associated with reduced content of some hepatic cytochromes.

Drug distribution can also be affected by oedema secondary to chronic heart failure and by ascites secondary to cirrhosis. The clinical drug exposure in a patient is not influenced by the plasma protein binding. Except in rare cases of intravenous drugs with high extraction ratio and narrow therapeutic index, there is no need of adjustment in dosing regimens.

The bioavailability of the orally administered drugs can be affected by the morphological and functional changes such as delayed gastric emptying, reduced splanchnic blood flow and altered gastric pH.

The plasma half life of drugs eliminated by kidneys can be increased by impairment in renal blood flow, glomerular filtration rate and capacity of renal tubular secretion.

Pharmacodynamics is mainly affected by immune senescence, physical ability to deal with infections and also the ability to deal with severe infections functionally and cognitively. As a result, there may be differences in clinical effects of younger and elderly patients.

2.1. BETA-LACTAM ANTIBIOTICS

Evidences says that the age can affect the pharmacokinetics of beta lactams. In elderly patients, the effect is mainly mediated by reduced renal clearance. About 33% of the renal function is reduced by the systemic exposure to Ceftaroline. Through urine, 70% of the Meropenem is excreted from the body and the creatinine clearance is significantly correlated with

Meropenem clearance. In case of nosocomial pneumonia, the pharmacokinetics of Doripenem is specifically studied in elderly patients: on comparison with young healthy subjects, the area under plasma concentration-time curve (AUC) was higher and the elimination half life ($t_{1/2}$) was longer in elderly patients. New drug studies of Avibactam says that $t_{1/2}$ was longer and maximum concentration (C_{max}) was lower in elderly male subjects in comparison with younger ones. At least, renal function of the elderly patients should be considered for dosages. In case of other newer antibiotics specific considerations have yet to be developed.

2.2. FLUOROQUINOLONES

The AUC_{0-24}/MIC ratio decides the antibacterial effectiveness of Fluoroquinolones. The Fluoroquinolone pharmacokinetics in the elderly patients has revealed a strong relationship of creatinine clearance and body weight on population analysis. If bacteria have low MICs, the dose reductions based on renal function is well adapted in elderly patients. Also, in case of patients with moderate or severe renal impairment and infection caused by strains with $MIC > 1 \text{ mg/L}$, a dosage reduction cannot allow an optimal exposure, with risk of suboptimal treatment.

2.3. VANCOMYCIN

One of the risk factors for Vancomycin induced nephrotoxicity is increasing age. Up to 90% of the Vancomycin is excreted through urine, when renal function is normal. So the Vancomycin clearance is correlated with creatinine clearance. There is an evaluated risk in elderly patients for nephrotoxicity with high ($> 15 \text{ mg/L}$) rather than low ($< 15 \text{ mg/L}$) average trough levels. Using Bayesian approaches, Bourguignon et al. built and validated a Vancomycin pharmacokinetic model for patients aged > 80 years. And they found high interindividual variability in pharmacokinetic parameters in this specific population. The daily AUCs should be maintained between 400-600 mg/L to maximize efficacy and minimize the chance for nephrotoxicity, based on the current best available evidence.

2.4. DAPTOMYCIN

On comparing the pharmacokinetic parameters of Daptomycin, there were no significant difference in the C_{max} and V_d of young adults (18-30 years) and the elderly (> 75 years)

volunteers. But the extent of exposure of Daptomycin was higher in elderly subjects. The changes in the renal function can cause changes in the pharmacokinetics of Daptomycin in elderly patients, with its lower excretion in the urine.

2.5. LINEZOLID

The body weight and age is correlated with the AUC_{0-24} of Linezolid. It shows a tendency to increase as body weight decreases and age increases. In recent pharmacokinetic studies, a 20-fold interindividual variation in antibiotic trough concentrations, with a positive correlation between Linezolid trough concentrations and patient age, for patients treated with a dose of 600 mg twice daily was found. The most important predictors of Linezolid toxicity are baseline platelet count and therapy duration of > 10 days. However, there is no clear recommendation on how to adjust the Linezolid dose in elderly to avoid overexposure of the drug.

2.6. GENTAMICIN

Effect of aminoglycosides in the elderly population have no recent studies. Despite the fact that Gentamicin has negligible protein binding, the larger V_d and lower C_{max} of Gentamicin is related with low albumin concentrations. The clearance of Gentamicin is totally correlated with creatinine clearance, even though the AUC/MIC is promoted as the best predictor of response for aminoglycosides. Thus, for avoiding nephrotoxicity in the elderly population, TDM, dose adjustment, short treatments and avoiding other nephrotoxic drugs can be useful.

2.7. COLISTIN

Because of the increase in bacterial resistance owing to the spread of multidrug-resistant (MDR) gram-negative bacteria, Colistin which is an old antibiotic has recently re-emerged. Using modern methodology, the pharmacokinetic studies of Colistin showed large interindividual variability in Colistin levels, associated with nephrotoxicity and with efficacy.

III. ROUTE OF ADMINISTRATION

Oral administration of the antibiotics can be suitable in the elderly but this route is ineffective in patients who are seriously ill due to the gradual rate of absorption from the gastrointestinal tract. Moreover, many of the antibiotics used in such patients are not available as

oral formulations. The other factors that can affect are non-compliance, altered gastric pH and delayed gastric emptying,

The intravenous (IV) administration of drugs can be used for the rapid delivery of the drugs but come with a risk of haematomas and phlebitis. It is further complicated for patients under anticoagulant or antiplatelet therapies.

The intramuscular (IM) route is more convenient since it can be performed at home. Antibiotics like Penicillin and Ceftriaxone are administered through the IM route. Skin tears and abscess formation can be the risk factors for this route.

The medications like Morphine Succinate and Midazolam are administered through the subcutaneous route. It is safer and less time consuming to perform in place of the intravenous and intramuscular routes.

IV. ANTIBIOTIC USE IN SPECIFIC POPULATIONS

4.1. IN ELDERLY PATIENTS WITH RENAL IMPAIRMENT

Appropriate prescription and rational use of antibiotics is vital in the elderly patients with chronic kidney disease, in order to ensure the safety and efficacy. The doses should also be adjusted accordingly in this population. The objective of maintaining the optimal pharmacodynamic targets can be a challenging task for the physicians. Various studies reveal that approximately 20% of the people above 60 years are diagnosed with CKD.

All these facts point to the necessity of the optimal use of antibiotics in the elderly, which can be performed by the assessment of the renal function in the geriatric patients. There are no clear evidences to state that any of the equations give an accurate estimation of the creatinine clearance (CL_{cr}) in these patients. However, the Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiologic Collaboration (CKD-EPI) are the formulae used. Newer equations like Full Age Spectrum and Berlin Initiative Study are used for the assessment of the glomerular filtration rate (GFR), each with its own limitations. Ideally, the creatinine clearance must be directly measured to avoid the irrational use.

4.2. In Elderly Patients With Hepatic Impairment

There has been extensive reviews on the prescription of the antibiotics in the elderly cirrhotic patients due to alterations in their pharmacokinetics. Even the pharmacokinetics of those antibiotics (β -lactams) which do not undergo hepatic metabolism are also affected by liver diseases. This may be due to the changes in the volume of distribution (V_d) (oedema, ascites) or alterations of the renal function in hepatic impairments. However, the pharmacokinetics of lipophilic drugs (Macrolides, Tetracyclines) is unaltered as they are widely distributed in the tissues, unaffected by the volume of distribution.

Better outcomes have been pointed out by many studies, by the administration of β -lactam antibiotics as continuous infusion. However, there are no many studies that predict the antibiotic dosages in elderly patients with hepatic impairments. Generally, the Child-Pugh score is being used for the dosage adjustment.

V. ADVERSE EFFECTS OF ANTIBIOTICS IN GERIATRIC POPULATION

The risk of occurrence of adverse effects of antibiotics is greater in the elderly, due to the comorbidities present. For example, those patients with the disorders of the cardiovascular system are more susceptible for the cardiac side effects of the antibiotics. Along with it, the presence of polypharmacy can also lead to several adverse effects due to the interactions of the antibiotics with the other drugs prescribed.

- There is a risk of Stevens Johnson syndrome with the use of Fluoroquinolones.
- Thrombocytopenia was found in 24% of the elderly patients treated with Linezolid.
- Nephrotoxicity is associated with the use of Vancomycin and Aminoglycosides in the elderly population.
- Greater the risk of neurotoxicity with Macrolides and Cephalosporins.

VI. RESULT

- Increased incidences of polypharmacy can lead to non-adherence of the elderly people to the medications. Polypharmacy can also pose a risk greater than that of the individual drugs alone.
- Various studies have detected the effects, antibiotics can have on the geriatric population.

Antibiotic	Type of Study	Result
Macrolides	Retrospective Gandhi S et al	Greater risk of acute kidney injury when co-prescribed with calcium channel blockers
Fluoroquinolones	Prospective Daneman N et al	Higher risk of tendon rupture
Vancomycin	Retropective Hall RG et al	Nephrotoxicity in 32% of patients
Linezolid	Retrospective Bi LQ et al	Thrombocytopenia in 24% of patients
Colistin	Retrospective Temocin F et al	Nephrotoxicity in 48% of patients

VII. DISCUSSION

Antibiotics are commonly prescribed in the hospitalized elderly patients. According to the study conducted by Binit N. Jhaveri et al, Cefotaxime was found to be the most frequently prescribed antibiotic. Majority of the geriatric patients with comorbid conditions like cardiovascular diseases were prescribed antibiotics, prophylactically.

Many of the antibiotics were primarily prescribed, empirically. So attempts should be made to promote the culture and sensitivity testing prior to the antibiotic use to prevent the antibiotic resistance and to monitor the optimal levels.

VIII. CONCLUSION

The antibiotic consumption in the elderly population is more than that in the younger patients. Because of the incidence of polypharmacy and higher prevalence of chronic diseases in this population, the chances of adverse reactions to the antibiotics are also greater. Thus, there should be a thorough and careful knowledge of the pharmacokinetic and pharmacodynamic aspects of these drugs. Studies should be initiated to promote a rational use of antibiotics and to individualize the antibiotic therapy in the geriatric population.

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