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DRUG INTERACTIONS AND POLYPHARMACY ON ANTIMICROBIAL THERAPY IN GERIATRICS PATIENTS- A REVIEW

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ABSTRACT

Infections are more common in the geriatric population than in younger adults, which is usually associated with higher morbidity and mortality. Besides, as people age, the risk of developing chronic health diseases becomes higher and leads to polypharmacy. When antimicrobial therapy is needed, it further increases the risk of drug-drug interactions between antimicrobial agents and concurrent medications. Antimicrobial agents are categorized under several classes according to their different mechanisms of action. Hence, the type of drug interactions varies. In this case, drug pharmacokinetics and pharmacodynamics should be considered in elderly due to their comorbid conditions. For instance, aging is associated with reduced gastrointestinal motility, altered body composition and impaired renal function, which may impact the antimicrobial therapy negatively. Additionally, polypharmacy together with antimicrobial regimen can increase healthcare costs and decrease medication adherence. Thus, the intervention of healthcare providers is crucial to optimize medication use among the older population. Educational intervention from physicians and pharmacists can improve patient adherence to their medications. Medication history taking should be performed to detect any possible drug interactions with antimicrobial agents. Antimicrobial stewardship program is a good approach to minimize the risk of antimicrobial resistance and overuses. Clinical trials regarding the use of antimicrobials which focus among geriatric patients with polypharmacy regimens are needed to provide safety data and improve national guidelines.

INTRODUCTION

Antimicrobial agents are widely used as therapeutic drugs and can be classified in terms of bactericidal and bacteriostatic agents. Bactericidal drugs can cause disruption and cell death of the bacteria by acting on the cell walls such as beta-lactam, cell membranes such as daptomycin as well as bacterial DNA such as fluoroquinolone. In contrast, bacteriostatic drugs can inhibit the further replication of the bacterial cell without killing the bacteria. Sulfonamides, tetracycline, and macrolides are examples of bacteriostatic drugs. A single-agent antimicrobial therapy is commonly used as first-line therapy but a combination of two or more antimicrobial agents is preferred in some conditions. Polypharmacy in term of antimicrobial therapy is not only able to increase the effectiveness based on different mechanisms of action, but also can reduce the risk of developing antimicrobial resistance. (Surnbhi, Chistine L. & Randall S., 2011) Polypharmacy is the use of multiple drugs to treat many types of diseases. Geriatric patients are the common population involving in polypharmacy due to aging. Generally, polypharmacy can result in adherence problems

among elderly patients. (Manouchehr, 2019) It becomes a concern for elderly as they have a greater risk for adverse drug reactions due to the metabolic changes and reduced drug clearance. The multiple drugs can increase the potential of drug-drug interaction which becomes problematic due to the negative outcome. Chance of getting adverse drug events is approximately 15% when taking two medications and further increases the chances of adverse effects to 58% when taking five medications. It can increase up to 82% of the risk of getting adverse drug effects when taking seven or more medications.In order to reduce the adverse effects of polypharmacy medication regimens in elderly patients, a single drug should be prescribed for the treatment instead of multiple drugs if possible. The medication can start with a lower drug which is clinically indicated and only increases if required. The drugs given once or twice per day are preferred than drugs given three times per day. (Alpert & Gatlin, 2015; Rushabh J & Akanksha, 2014)

The problems of drug-related issues can arise in older adults such as the ineffectiveness of drugs, adverse drug events, drug-drug interactions and over or under dosage. The ineffectiveness of drugs might be due to under dosing because of the concern in adverse drug effects and poor adherence towards medications such as financial problems. Adverse drug events can cause danger and uncomfortable states to people such as confusion and oversedation. In older patients, the hospitalization rates might increase four times higher about 17% because of adverse drug effects as compared with younger patients with 4%. Approximately 66% of hospitalization of older adults might be due to drug classes which include insulin, warfarin, oral hypoglycemic drugs and oral antiplatelet drugs. However, adverse drugs can happen in any patients, but it is more susceptible to older patients. (Ruscin & Linnebur, 2018a)

As the aging growing population increases, the pharmacokinetics and pharmacodynamics will deteriorate gradually in elderly adults as compared to younger and middle-aged adults. Pharmacodynamics is defined as the drug response to the body.It can be influenced by the binding to receptor, post-receptor effects and interaction of chemicals.(Ruscin & Linnebur, 2018b)Pharmacokinetics is defined as how the body reacts to drugs. It includes absorption, distribution, metabolism and excretion. The metabolism and excretion process will get affected with aging and the problems in metabolizing and excreting drugs will arise. This is due to more accumulation of drugs and slowly develops into toxicity and causing harm to the body. Thus, some adjustments in dosing of drugs are required in elderly people. (Ruscin & Linnebur, 2018c)

The physiological changes in the body can be predicted in aging people regarding pharmacokinetics and pharmacodynamics. It can predict approximately 40% of older adults having problems in reduced renal blood flow and glomerular filtrate rate. However, it varies among individuals. In addition, changes in liver volume can occur in aging people. The liver function impairment associated with aging could compromise the first-pass metabolism in the liver of the medications. Furthermore, some medications will have a higher affinity for albumin. However, in aging people, it found approximately decreases around 15% to 20% in serum albumin and might even lower if associated with illness. (Alpert & Gatlin, 2015)Apart from that, geriatrics patients will have a higher risk of acquiring drug-resistance in bacterial infection because of more frequent and prolonged contact with the healthcare system, impair immune function due to chronic disease as well as the gradual deterioration of the immune system due to aging. Antimicrobial therapy is crucial in helping to prevent morbidity and mortality due to infection. The importance of understanding the drug-drug interaction in elderly and the pharmacokinetics and pharmacodynamics of drugs in geriatrics patients due to comorbid conditions and the normal physiological changes related to aging. Thus, healthcare providers should be aware of the consideration and consequences before giving the antimicrobial pharmacotherapy to geriatrics patients. (Angela, Samantha EL & David P, 2018)

Drug interactions and polypharmacy on antimicrobial therapy in geriatrics patients

Drug-drug interaction (DDIs) in geriatric patients

National Medical Care Survey (NMCS)is a national cross-sectional survey which were primarily conducted in Malaysia. They have collected the responses from 22,832 geriatric patients who visited the primary care clinics. Based on the National Medical Care Survey (NMCS), a total of 20.3% in 22,832 geriatric patients experienced polypharmacy. (Ong et al., 2018) Geriatric patients describes patients with aged ≥65 years while polypharmacy refers to the administration of ≥ 5 medications. The risk of drug-drug interactions raises by 75% among the geriatric patients who experienced polypharmacy. The practices of polypharmacy had also given rise to 12% of hospitalization in the older person. Undeniably, it also indirectly leads to the poor adherence and the elevation of healthcare costs which burdens the older person.(Ong et al., 2018) All in all, it has also contributed to the mortality rate in elderly.

Polypharmacy is said to have an undesirable therapeutic outcome if it is not well- managed as it was reported that polypharmacy is greatly associated with drug-drug interactions and the occurrence of adverse drug reactions. Particularly, the usage and dosage of medication use in geriatric patients should be taken into concern as they have a greater prevalence of polypharmacy. (Kim et al., 2014) The failure adjustments to the dosage for patients with renal dysfunction had also contributed to the adverse drug effect in the antimicrobial treatment. Thus, dosage adjustments are highly required particularly for > 85 years old patients. (Carmen M. F, Heather LC, and John C. W, 2005). There were a few considerations and principles to adhere in prescribing the antimicrobial drugs to the geriatric patients. It is advisable to narrow the empirical broad-spectrum antibiotics once the pathogen is identified. This can minimize the chances of resistance of microbes. The credo "start low, go slow" were practiced by many practitioners in initiating antimicrobial therapy in older person. This is because aged people tend to acquire immunosenescence, comorbidities and experience physiologic change. (Faulkner et al., 2005) This can lead to the alteration of bioavailability of antimicrobial drugs. Therefore, the choice,dosage, timing and frequency of drugs should be carefully studied before prescribing the drug to achieve the therapeutic goal.

Tetracycline:

Tetracycline is a chelating compound that possesses carboxylic and phenolic functional groups. Studiesshown that it is able to form strong complexes with various cations such as aluminum, calcium, iron, or magnesium in solution. It results in the formation of strong cations complexes. Thus, it decreases the absorption of tetracycline and effectiveness of tetracycline. (Gu & Karthikeyan, 2005)Antacids should be particularly avoided with the administration of tetracycline as it is composed of aluminum calcium and magnesium. Additionally, aluminum, calcium, iron, or magnesium form of supplements will also interact with the tetracycline.

Macrolide:

Macrolide such as erythromycin,clarithromycin, azithromycin can interact with the digoxin. Digoxin is cardiac glycoside class of drug. It has a high-affinity substrate which binds at the P-glycoprotein, which helps in the elimination of drugs. Macrolides antibiotic tend to cause inhibition of P-glycoprotein. It changes the gastrointestinal flora, reduces the digoxin transport into the intestinal lumen and contributes to the increase in oral bioavailability of digoxin. It may also increase the risk for digoxin toxicity.(Hines & Murphy, 2011)

Aminoglycoside:

The aminoglycoside class includes the Amikacin, Gentamicin, Netilmicin,Neomycin, Streptomycin, Tobramycin. The administration of aminoglycoside can cause nephrotoxicity as it leads to the damage of the kidney tubules. Amphotericin B,cyclosporin, cisplatin, loop diuretics, tacrolimus, and vancomycin are inherently nephrotoxic. The administration of aminoglycoside with these drugs can result in synergistic nephrotoxicity. (Naughton CA, 2008) In other words, additive nephrotoxicity and the risk of renal injury will increase greatly as well.

The pharmacokinetics of geriatric patient

Absorption: According to Goldacre, the probability of gastrointestinal (GI) disorder increases with aging.(Goldacre, 2009) Besides,

insignificant changes in the GI tract is observed.(Bhutto & Morley, 2008) Various studies showed that the decrement of gastric acid secretion provoked the rise of gastric pH occurs along with aging.(Shi and Klotz, 2011) Geriatric patients taking proton-pump inhibitor or antacids interrupts the ionization of drugs. (Andres et al., 2019) Increase in gastric pH can ultimately change the solubility and stability of some antimicrobial drugs such as beta-lactams and macrolides, hence decreasing their bioavailability. (T. Mazzei, 2011) GI motility decreases with an increase in age.(Shimamoto et al., 2002) The absorption of orally administered drugs is affected which in turn influences the bioavailability of the drugs especially for those antimicrobial drugs which are taken with or after meals such as amoxicillin with clavulanic acid. Undesirable side effects are the outcome when the duration of the drugs exposed to the GI tract is sustained especially for low solubility drugs.

Distribution:

The body composition altered with the increase in ageas shown in Figure 1. The decrease in total body water affects the distribution of hydrophilic drugs such as aminoglycosides and increases the plasma concentration of the drugs. Hence, lower initial doses of antimicrobials are required to avoid adverse drug events. Conversely, due to the increase in body fat, lipophilic drugs which are non-polar in nature have a higher distribution volume. The half-life of the drugs is extended and thus, increases the probability of drug-drug interaction and leads to unwanted consequences. (Klotz, 2009)

Metabolism:

Liver is the main organ involved in metabolism.Based on a study conducted by McLean AJ, around 40% of hepatic blood flow reduces in the elderly. (McLean & Le Couteur, 2004) The decrease in liver function increases the half-life of antimicrobial agents such as macrolides metabolized by the liver. Besides, various metabolic enzymes are found on the intestinal wall, metabolism also occurs on the intestinal wall. Any changes that occur on the intestinal wall affect the efficacy of the drugs. Polypharmacy may increase the chance of drugs competing for metabolic enzymes, cytochrome P450 (CYP) present in the liver. (Angela, Samantha EL & David P, 2018)

There are many antimicrobial agents which undergo metabolism in the liver, comprising of both phase I oxidation and phase II conjugation. These processes are important to increase the hydrophilicity of drugs for renal excretion. The metabolic processes in antimicrobial agentssuch as fluoroquinolones, macrolides, and antifungal azoles are greatly influenced especially in geriatric patients with impaired hepatic function (T. Mazzei, 2011)

Excretion:

Most antimicrobials such as aminoglycosides and penicillin are excreted via kidney. The decrease of renal function indicated by the decrease of renal mass and renal blood flow is observed in elderlies. Besides age, renal impairment is found in patients with hypertension or other cardiovascular diseases. This causes drug accumulation to occur as the elimination processes are hindered. The plasma concentration of the drugs increased causes toxicity and thus, leads to undesirable effects.(Andres et al., 2019).For instance, all parent drug or metabolites of tetracycline except doxycycline are reabsorbed in the intestine and excreted in kidney. This should be concerned among the geriatric patients especially those with renal impairment.Accumulation of tetracyclines can reduce protein synthesis in host cells, causing antianabolic effect that may worsen the damage in kidney.

Consequence of polypharmacy and Intervention to reduce the drug interaction:

The consequences in relation to polypharmacy are related to drug utilization. This is due to increases the numbers of drug used can potentiate drug-drug interaction.The outcomes can categorize into four according to theoretical proximity to polypharmacy.It can be observed the inner circle are the most nearest to polypharmacy which includes drugs related outcomes. While moving to the outer circle, the outcome may be due to more proximal outcome which ends up in hospitalization due to drug-drug interactions.The figure 2 of framework for polypharmacy and the classification of outcome can be shown as

below:(Wastesson, Morin, Tan & Johnell, 2018)

Increased Healthcare Costs

Increased frequency and amount of taking multiple medications may cause a burden to both patients and the healthcare system in the healthcare cost.Polypharmacy may result in an increased risk of taking inappropriate medication, increased in the frequency of outpatients visit as well as hospitalization that contributes around 30% increase in medical cost.Based on the study carried out in Sweden, it had reported taking 5 or more medications contributes to 6.2% increase in drug expenditure while taking 10 or more medications contributes to 7.3% increase in drug expenditure.(Robert L, Joseph T & Emily R., 2014).

Table 1: Drug interactions among antimicrobials prescribed to elderly (Faulkner et al., 2005)

Antimicrobial Class	Antimicrobial agent	Interacting Agents
Tetracycline	Tetracycline	Agent containing aluminum, calcium, iron, or magnesium; antacids; and bismuth subsalicylate
Macrolide	Clarithromycin, Erythromycin, Azithromycin	Digoxin
Aminoglycosides	Amikacin Gentamicin Netilmicin Neomycin Streptomycin Tobramycin	Amphotericin B, cyclosporin, cisplatin, loop diuretics, tacrolimus, and vancomycin

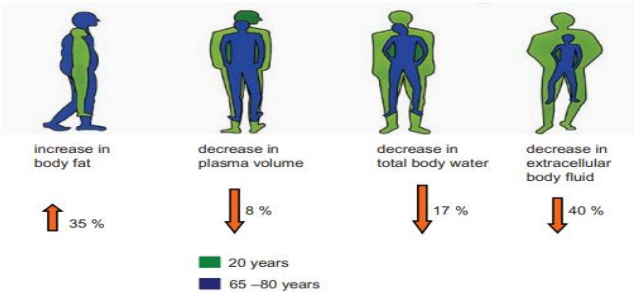

Figure 1: Variation of body composition based on age. (Klotz, 2009)

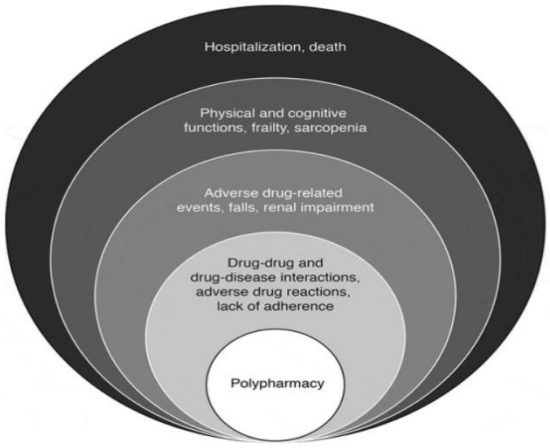

Figure 2: Framework for polypharmacy associated with outcomes (Wastesson, Morin, Tan & Johnell, 2018)

Table 2: Physiological changes in geriatric patients and impact on pharmacokinetics (Shi and Klotz, 2011)

Parameter	Changes	Effects on drugs pharmacokinetics
Absorption	Reduced gastric acid secretion Increased gastric pH Decreased gastrointestinal motility	Decreased drugs dissolution rate Decreased bioavailability of drugs Decreased absorption
Distribution	Increased body fat	Increased half-life of lipophilic drugs
	Decreased body total water Decreased lean body mass	Decreased distribution of hydrophilic drugs
Metabolism	Decreased hepatic flow	Reduced first-pass metabolism Increased half-life of drugs
Excretion	Decreased renal blood flow Decreased renal function	Increased half-life of drugs Reduced renal excretion of drugs Drug accumulation in plasma Increased risk of drug toxicity

Cognitive Impairment

Cognitive impairment is associated with a decline in cognitive status and can be seen in both delirium and dementia. It also reported delirium are affected by the number of medications.Based on a prospective cohort study,10 or more medications, 6 to 9 medications, and 5 or fewer medications are shown in 54%, 33% and 22% of elderly patients respectively. (Robert L, Joseph T & Emily R., 2014) It is crucial to acknowledge the specific drug types. As it may bring negative outcomes in cognition associated with the utilization of drugs.(Wastesson, Morin, Tan & Johnell, 2018)

Adverse Drugs Event

It has been reported that nearly 90% of the elderly are admitted to the hospital due to adverse drug reactions.Based on UK studies, patients with chronic obstructive pulmonary disease (COPD) are taking multiple medications frequently which can lead to adverse drug reactions such as renal impairment and urinary retention. Drug regimen is complicated for patients encountered with polypharmacy and using several guidelines for a single disease.This will in turn lower medication adherence and raises in mortality rate. (Wastesson, Morin, Tan & Johnell, 2018)

Medication Non-adherence

It has been reported a majority of elderly patients feel burdened by their medication especially those with a higher number of medications prescribed. In addition, elderly patients with multiple comorbidities, increase in age as well as number of medications will cause false-thinking that the medications are not appropriate.(Omar MS, Ariandi AH & Tohit NM, 2019) There are studies proven that approximately 43-100% of non-adherence rates is due to complicated medication regimens as well as polypharmacy. (Robert L, Joseph T & Emily R., 2014)

Collaboration between physicians and pharmacists

Based on the studies by Wong et al, collaboration between physicians and pharmacists can improve patients' health outcomes through discussion. Based on the Medication Appropriateness Index (MAI), pharmacists can screen prescriptions to check the appropriateness of the medication for elderly patients. Thus, some unnecessary medications can be reduced to patients. Besides, counseling from both physicians and pharmacists can improve the patients regarding medication adherence and knowledge about their medication.(Shim YW, Chua SS,Wong HC & Alwi S, 2018)

Future Prospects: In most of the cases, polypharmacy is inevitable among geriatric patients in consideration of their deteriorating health conditions and multiple diseases. Hence, all healthcare professionals including pharmacists play a crucial role in optimizing their concurrent medication uses especially with the addition of antimicrobial therapy. Medication history taking should be performed before starting the antimicrobial therapy in geriatric patients in order to get information

with regards to their concurrent drugs used and chronic conditions. This helps to avoid drug-drug interactions from happening by selecting antimicrobial agents wisely. The information about their previous antimicrobial therapy, if any, can also help the healthcare providers to identify the antimicrobial resistance and effectiveness in the patients. Apart from that, all healthcare professionals should practice good antimicrobial stewardship fundamentally in future. It is an approach by healthcare commissioners including pharmacists to promote and optimize the antimicrobial drug regimen in order to minimize the risk of antimicrobial resistance and preserve their future effectiveness. Antimicrobial stewardship programme can reduce health complications, improve outcomes and limit healthcare costs among elderly patients especially those with polypharmacy, by avoiding antibiotics overuses and drug interactions. (Pharmaceutical Services Division committee, Ministry of Health, 2014).

Other than that, healthcare professionals should take into consideration the principle of drug pharmacokinetics and pharmacodynamics in elderly patients carefully during the polypharmacy and antimicrobial regimens. Contraindication of antimicrobial agents should be taken into consideration for elderly with impaired organ function. For instance, geriatric patient with impaired renal function should avoid taking tetracycline antibiotics. Instead, only doxycycline among tetracycline class can be given because they are excreted as feces but not urine, so accumulation in kidney can be avoided. As concurrent use of different medications may influence the physiological effects in the body, a correct dose of antimicrobial drugs within the therapeutic window should be modified for each different patient to ensure the effectiveness and avoid any adverse side effects. Geriatric patients should be closely monitored throughout the antimicrobial therapy. It should be discontinued as soon as possible after another strain of pathogen is identified or the elderly has been recovered from infection. On top of that, clinical research regarding the use of antimicrobials by focusing among the geriatric population with polypharmacy can be conducted in the future to provide a more detailed and systematic study in this topic. Generally, the elderly with co-morbidity are usually excluded from clinical trials. Most of the studies were only focused on particular diseases. However, as mentioned above, the older population has various health conditions such as impaired immune system, impaired functions in different organs and hence, different chronic disorders. Thus, particular clinical trials about the use of antimicrobials in these various conditions should be tested to improve safety, especially those with impaired renal function as they are more prone to adverse drug events. Drug interactions that have not been discovered can be potentially identified via studies. This may ultimately improve the guideline on the antimicrobial therapy among the geriatric patients involved in polypharmacy.

CONCLUSION

In conclusion, the occurrence of drug-drug interactions is treatment-related and patients age-related. Geriatric patients should consult and inform their physicians honestly with all the medications they were taking. Various age-related changes in physiology are found which will affects the pharmacokinetics profile of geriatric patients. Other than that, comorbidities and polypharmacy may cause undesirable side effects due to unwanted interaction between drugs. In addition, it brings a burden to both patient and healthcare system cost.The utilization of multiple medications can lead to cognitive impairment in elderly. Therefore, cooperation between physicians and pharmacist are encouraged to ensure good patient health outcomes and reduces any unnecessary medications.In order to provide a good antimicrobial therapy in the future, antimicrobial stewardship programme is one of the ways to optimise the antimicrobial drug regimen to reduce the risk of antimicrobial resistance and enhance future effectiveness.The principle of drug pharmacokinetics and pharmacodynamics in elderly patients should monitor carefully to prevent from exposing to the pathogen and antimicrobial therapy should be halt and reviewed if found another strain of pathogen or patient had fully recovered. Clinical research should be carried out in the future to provide a detailed and systematic study focusing on the geriatric population with polypharmacy.

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