Review Article

Pharmacokinetic Changes in Congestive Heart Failure

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ABSTRACT
Pharmacokinetic processes are recognized as "liberation, absorption (A), distribution (D), metabolism (M) and excretion (E)". Published ADME data for each drug are usually observed on healthy individuals. It serves as an indispensable guide to prescribers. LADME guides highlight the significant role of the gastroenterology system, hepato-biliary system, cardiovascular system and renal system. Any changes in the structure and function of these systems would lead to variations in the ADME system. The existence of individual differences and pathophysiological status of major organs further affects the clinical pharmacokinetic profile of drugs. Therefore, unpredictable variations in pharmacokinetic parameters may exist in patients suffering from diseases of the heart, the liver or the kidneys. Most importantly, the deviation of pharmacokinetic parameters could affect the outcome of the management of the disease. Of these organs, the heart is a very crucial one as the circulation is the main transport route for the passage of drugs through the body. Congestive heart failure is a common cardiac disease in both the well-developed and the developing countries. The pathophysiology of congestive heart failure has already been complicated with hemodynamic abnormalities, neurohumoral mechanisms and the damage to the cardiac muscle itself. As congestive heart failure is more commonly seen in the elderly patients, age-related changes should also be considered. The objective of this article is to facilitate the better management of congestive heart failure, based on evidence-based information on pharmacokinetic changes, to make dosage adjustment of the right drug for the right patient, with minimal adverse effects.
Keywords – *clinical pharmacokinetic, congestive heart failure, pharmacokinetic changes, drug metabolism, drug absorption, drug elimination.*

INTRODUCTION

Medical professionals have learnt how to choose the right drug for the right patient with the right reason. Generally, the dose of the medicine is available in the management guidelines. This may be applicable for most of the patients. But is it the right dose for every patient?

Careful adjustment of the dose or dosing frequency is often required when it comes to treating patients with inter current illnesses. For such patients,

treatment need to be based on understanding of the principles of clinical pharmacokinetics.

Although the pharmacokinetic profile has already been studied prior to the registration of a new drug, actual clinical situation could lead to a deviation from the reported values. The individual pharmacokinetics could differ from population kinetics. Pathophysiological changes due to co-morbid diseases impose an additional burden on the pharmacokinetic parameters.

Therefore, it is a logical assumption that pharmaco-kinetic of drugs would be altered in patients with congestive heart failure.[1] Pharmacokinetic changes of drugs in heart failure are not very predictable due to various changes in haemodynamic.[2]

Heart failure is a systemic low-perfusion syndrome which is usually a consequence of impaired cardiac output.[3]It is further complicated with low systemic pressure, reduced organ blood flow, altered gastrointestinal motility, increased venous pressure, activation of neurohumoral mechanisms, and increased total body water. These alterations would lead to toxicity for some drugs and sub-therapeutic effect or therapeutic failure for others.

If reduced organ perfusion occurs at the site of clearance (e.g. liver and kidney), drug clearance is affected. Because of increased venous pressure, organ congestion can occur in liver and gastrointestinal tract. Consequently, there will be changes in volume of distribution and metabolism or clearance.[2]

This article conveys the importance of clinical pharmacokinetic changes in heart failure in order to avoid unintended effects while achieving the optimal dose for individual therapeutics.

OBJECTIVES

The objective of this review is to study the clinical pharmacokinetic changes under congestive heart failure. It is aimed to facilitate better management of congestive heart failure, with optimal dosage adjustment of the right drug for the right patient, and with minimal adverse effects.

CHANGES OF PHARMACOKINETIC PARAMETERS IN CONGESTIVE HEART FAILURE
CHANGES IN DRUG ABSORPTION

Hypo-perfusion of gastrointestinal tract is usually seen in congestive heart failure. The absorption of most drugs is dependent on gastrointestinal blood flow. But large amount of reduction in mesenteric blood flow is required to cause a significant decrease in drug absorption. Therefore, physiological variability of reduction or increase in mesenteric blood flow is rarely a rate limiting step for absorption of majority of drugs.[4]

There is also increased venous pressure in congestive heart failure. Due to increased venous pressure, there will be gastrointestinal tract congestion and results in wall oedema.Gut wall oedema causes reduced epithelial permeability. Reduced epithelial permeability impairs absorption of drugs and essential nutrients in heart failure patients.[1]In studied CHF patients, there was abnormal absorption of fat which could be improved by diuretic administration.[5]

Absolute amount and rate of absorption of loop diuretics were decreased in heart failure and it was found that dissolution characteristics of the drug was an important factor.[1] Furosemide had a wide variation in intra and inter-patient variation in absorption characteristics but torsemide was nearly completely absorbed regardless of the heart failure state.[1]This difference in absorption characteristics for torsemide makes it beneficial for the important use in diuretic-resistant heart failure patient.[1]

Congestive heart failure would have an impact on absorption of oral as well as intramuscular drugs. [1, 5]

Intravenously administered drugs do not have much changes (either no or minimal) in states of congestive heart failure, inclusive of asymptomatic heart failure to compensated chronic heart failure and the patients who had no co-morbidities like hepatic or renal insufficiency.[3]

The related pathophysiology and consequences leading to changes in pharmacokinetic of drugs are collectively summarized in figure 1 below.
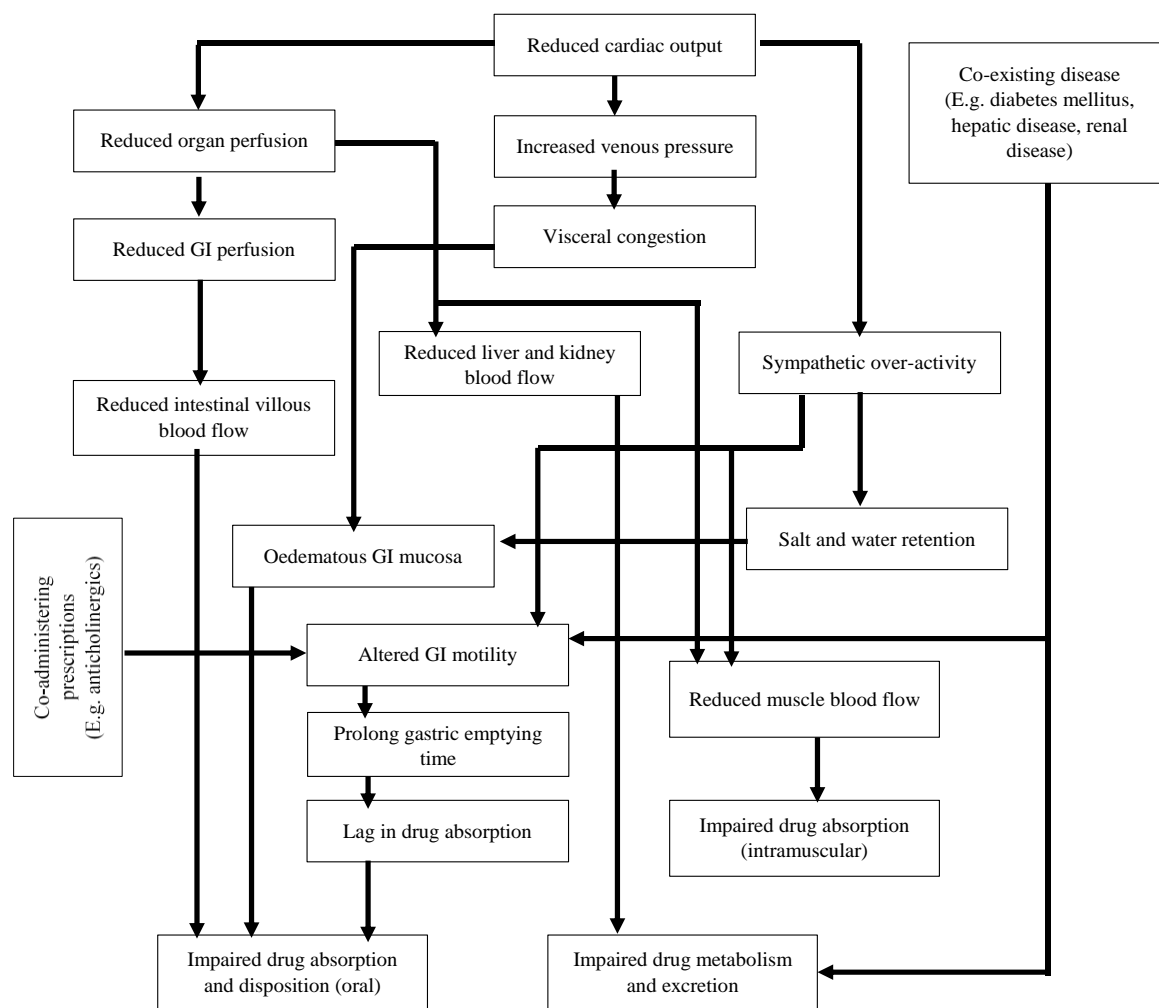
Figure (1) Diagram showing the pathophysiological consequences of congestive heart failure leading to impaired drug absorption, disposition, metabolism and excretion

(Oral and intramuscular)

(Summarized from Benowitz and Meister (1976)[6] and Sica (2003)[1])

Interestingly, posture of the patient was found to be an additional factor which could influence diuretic effect. Attenuation of subsequent natriuretic response was seen when the congestive heart failure patient took a loop diuretic in the upright position.[7,8] Furthermore, this posture related reduction effect fades when enalapril (angiotensin converting enzyme inhibitor) is co-administered with intravenous furosemide.[8] This interaction of posture, ACE inhibition, and loop diuretic effect has not been explored with oral loop diuretic therapy.[1]

Age-related changes in gastrointestinal physiology might also affect the disposition, ionization and solubility of drugs. Age related changes includedecreased acidity in the stomach, decreased gastric emptying time, decreased gastrointestinal blood flow, atrophy of gastric mucosa and decreased gastric motility. These effects mostly would not besignificant enough to alter bioavailability of the drugs in the normal persons but would enhance pathophysiological changes of gastrointestinal tractin the elderly patients with congestive heart failure.[9]

CHANGES IN DRUG DISTRIBUTION

Plasma Protein Binding & Volume of Distribution

In patients with congestive heart failure, plasma albumin concentration would be within the normal range and stable if the nutritional status is balanced in the absence of concurrent hepatic or renal insufficiency.[3]

There might also be age related decrease in plasma albumin level.This effect could have an impact on Vd and free plasma drug concentration especially for acidic drugs.[9] Because of low plasma albumin level, the binding sites on plasma proteincould become saturated if the drug is highly plasma protein bound. Thiswould lead to higher free plasma drug concentration predisposing to development of drug interactions, increased incidence of adverse effects and toxicity.

Body responses to tissue damage and inflammation processes (e.g. myocardial infarction) causes an increasein alpha-1-acid glycoprotein (AAG).As such, acute decompensated heart failure could also cause increased AAG.[3]Therefore, plasma protein binding of basic drugs (e.g. lignocaine) would be increased resulting in decreased free plasma drug concentration. Cautionary measures such as dosage adjustment should be considered/practised to prevent sub-therapeutic effect or therapeutic failure. AAG level could increase in the elderly resulting in increased binding of basic drugs leading to sub-therapeutic response.[9]

When a drug possesses high plasma protein binding capacity, it will be distributed mainly in the intravascular compartment and hence the drug would have a low volume of distribution (Vd). Vice versa, if the drug has low plasma protein binding, it will have a higher Vd, and its distribution will be mainly inside the tissue.[3]Variation of apparent Vd on different drugs are presented in table1.

CHANGES IN TERMINATION OF DRUG ACTION

Clearance

Clearance is an important pharmacokinetic parameter for a drug. Systemic clearance (CL) mainly includes hepatic clearance and renal clearance.

If renal clearance is denoted as "CL_R" and the fraction of drug which would be eliminated through the kidney as unchanged form to that absorbed into the systemic circulation could be designated as "fR". The "fR" represents the ratio of renal clearance (CL_R) relative to clearance (CL). If the calculated fR is more than 0.7, the drug is assumed to be mainly excreted by kidney. If the fR is less than 0.3, it is assumed that elimination is mainly via hepatic metabolism and gastrointestinal tract (non-renal). In other words, for drugs with more than 0.7 fR, their area under concentration curve would be easily affected by renal insufficiency.[3]

Renal clearance

Renal excretion in the body was mainly determined by glomerular filtration rate (GFR) and renal blood flow.

Digoxin could lead to toxicity if the same dose was used between the agedand the young adults.[10] Excretion of atenolol, nadolol and procainamide was found to decline with age because these drugs were mainly excreted through the renal route.[11]These findings proved that even age-related reduction in renal function could have an impact on excretion of drugs.

Therefore, if cardiac output was decreased, there will be a further reduction in renal blood flow and GFR. In elderly CHF patients, age-related decline in renal function and co-morbidities like diabetes mellitus are additional factors to consider together with reduced cardiac output.

Serum creatinine level is usually used as a tool to assess the renal function. But serum creatinine level would not always be a reliable criterion for assessment of the renal function in the elderly. It was because serum creatinine might not increase markedly in the elderly people due to age related reduction in muscle mass. This could lead to less creatinine production and make the level somewhat similar in the old and the young.[9] Creatinine clearance test would be a better method for assessing the renal function in important situations. It could be measured by Cockroft-Gault equation[12] It was usually used to access the renal function for drug administration.[13]

According to Liu (2008)[14], trans-renal perfusion pressure can be calculated as follows:

Trans-renal perfusion pressure = mean arterial pressure − central venous pressure

In patients with heart failure, low systemic pressure can lead to low mean arterial pressure. At the same time, due to volume overload, increased central venous pressure would occur. Low mean arterial pressure and increased central venous pressure would lead to a severe compromise to net renal perfusion pressure. As a result, worsening of acute heart failure which precipitates worsening of renal function, and this could be the underlying pathophysiology of cardio-renal syndrome.[14]

Hepatic clearance

Enzyme activities and hepatic blood flow usually determine the hepatic clearance of drugs.[9]Even in healthy elderly population, increased response to drugs such as quinidine, warfarin and lignocaine could be seen because these drugs normally undergo extensive hepatic metabolism.[9]

Reduction in hepatic blood flow with reduced size of liver could affect phase I metabolism. For the drugs which undergo extensive hepatic metabolism, there could be a reduction in clearance. This leads to a longer plasma half-life with elevation in plasma concentration and increases the risk of toxicity. [15]Phase II reactions generally are not affected by age.[16]

In congestive heart failure, hepatic and intestinal drug-metabolizing activities were reduced. [1]Prodrugs (e.g. enalapril) would face delayed activation and there would be a lower concentration and/or delayed appearance in patients with congestive heart failure.[1, 17]

Because of decreased hepatic metabolism, drugs which have high pre-systemic elimination (e.g. prazosin and hydralazine) would have a higher plasma drug concentration.[18,19]In severe cardiac failure, theophylline dosage need to be reduced because the metabolism of theophylline is dependent on hepatic blood flow.[6]

Changes in plasma half-life

In a one compartment model, plasma half-life (T½)could be derived from plasma concentration time curve as well as by the following formula.[3]

$$T\tfrac{1}{2} = \frac{Log2 \text{ x } Vd}{Kel}$$

$T\tfrac{1}{2}$ = plasma half-life of a drug

V_d = volume of distribution

K_{el} = elimination rate constant

Again, as mentioned above, clearance of a drug is affected by organ blood flow (i.e. hepatic and renal). If there is reduction in drug clearance, plasma half-life would be prolonged because the two parameters are inversely proportionate. This pathophysiology could be seen in the congestive heart failure.

If the volume of distribution is increased, the plasma half-life of a drug will be increased because these two parameters are directly proportional. Increased volume of distribution could be seen in congestive heart failure states as well.

If clearance is decreased by any cause, steady state plasma concentration (Css) of a drug would be increased, provided that dosing rate remains constant. This is because dosing rate is the multiplication of clearance and steady state concentration. Increased Css can easily lead to toxicity. But unchanged plasma half-life does not always mean that V_d and clearance are within the normal range. If the changes of both V_d and CL are counterbalanced, there would be no change in plasma half-life at all.[3]

All in all, changes of organ perfusion (low cardiac output and changes in ejection fraction) and peripheral oedema as observed in the patients with congestive heart failure are unavoidable pathophysiological changes. This would result in tremendous changes in pharmacokinetics of administered drugs which can end up in overdose, toxicity or therapeutic failure even when using the right dose and the right drug.[3]Variations in clearance of different drugs in patients with congestive heart failure are presented in table (2).

Table (1) Findings of variation of apparent volume of distribution of different drugs in patients with congestive heart failure

Study drug	Parameter	Outcome	Subjects	Name of study
Lignocaine	Vd& clearance	Decreased	CHF patients	(Benowitz and Meister, 1976)[6]
Quinidine	Vd	Increased	CHF patients	
Aminopyrine	Vd	Increased in patients with congestive heart failure compared to normal control subjects	11 patients with congestive heart failure and 15 control subjects	(Hepner et al., 1976)[20]

Table (2) findings of variation of clearance of different drugs in patients with congestive heart failure

Study drug	Parameter	Outcome	Subjects	Name of study
Lignocaine and procainamide	clearance	Accumulation of active metabolites	CHF patients	(Benowitz and Meister, 1976)[6]
Digoxin	clearance	Lessened	CHF patients	
Aminopyrine	clearance	Impaired	11 patients with congestive heart failure and 15 control subjects	(Hepner et al., 1976)[20]
Aminopyrine breath test	clearance	Impaired with significant difference	11 patients with congestive heart failure and 15 control subjects	
Aminopyrine breath test	clearance	Increased aminopyrine breath test associated with clinical improvement with significant difference	8 CHF patients before treatment of acute heart failure and 10 days after initiation of therapy	

CONCLUSION

Changes of pharmacokinetic parameters are considered to be important for narrow therapeutic drugs (e.g. digoxin). In addition, due to pathophysiological changes of the underlying disease condition from time to time, cautious adjustment of loading dose and maintenance dose of drugs is also critical.[2]

The usage of drugs in elderly people always necessitates caution and it is more important when geriatric physiology is complicated by specific disease pathology. Congestive heart failure itself has many pathophysiological states: acute or chronic; compensated or decompensated.

Asymptomatic or compensated heart failure may not have much changes in pharmacokinetics unless the patient is complicated by other co-morbidities. Decompensated acute heart failure and symptomatic chronic heart failure usually have altered pharmacokinetic processes. Age related and disease related implications may worsen the clinical pharmacology of drugs used in heart failure.

Due to ethical reasons, the pharmacokinetic studies related to heart failure states may not have been done extensively especially for acute heart failure and symptomatic chronic heart failure. More attention should be paid for optimization of drug therapy for congestive heart failure patients (e.g. plasma drug concentration measurement). In any case, treatment of refractory heart failure should follow drug treatment guidelines, paying attention to alteration of pharmacokinetic parameters and adjusting the dosage regimen, rather than increasing the dose or adding a new drug. All in all, "primum non nocere" is the heart of our profession while updating the knowledge to our best.

REFERENCES

1. Sica DA. Drug Absorption in the Management of Congestive Heart Failure: Loop Diuretics. Congest Heart Fail 2003 Sep-Oct; 9 (5):287-92.

2. Shammas FV1, Dickstein K. Clinical pharmacokinetics in heart failure: An updated review. ClinPharmacokinet. 1988 Aug; 15(2):94-113.

3. Ogawa R, Stachnik JM, Echizen, H. Clinical Pharmacokinetics of Drugs in Patients with Heart Failure. Clin Pharmacokinet 2013; 52:169–85.

4. Carlton LD, Pollack GM, Brouwer KL. Physiologic pharmacokinetic modeling of gastrointestinal blood flow as a rate-limiting step in the oral absorption of digoxin: implications for patients with congestive heart failure receiving epoprostenol. J Pharm Sci. 1996; 85:473–77.

5. Berkowitz D, Droll MN, Likoff W. Malabsorption as a complication of congestive heart failure. Am J Cardiol. 1963; 11:43–47. (abstract)

6. Benowitz NL, Meister W. Pharmacokinetics in patients with cardiac failure. ClinPharmacokinet. 1976 Nov-Dec; 1(6):389-405.

7. Ring-Larsen H, Henriksen JH, Wilken C, Clausen J, Pals H, Christensen NJ. Diuretic treatment in decompensated cirrhosis and heart failure: effect of posture. BMJ. 1986; 292:1351–53.

8. Flapan AD, Davies E, Waugh C, Williams BC, Shaw TR, Edwards CR. The influence of posture on the response to loop diuretics in patients with chronic cardiac failure is reduced by angiotensin converting enzyme inhibition. Eur J ClinPharmacol. 1992; 42 (6):581–86.

9. Williams. Cardiovascular Drug Therapy in the Elderly: Theoretical and Practical Considerations. Drugs Aging 2003; 20 (6): 445-63.

10. Sumner DJ, Russel AJ. Digoxin pharmacokinetics: multi-compartmental analysis and its implications. Br J ClinPharmacol 1976; 3: 221-29.

11. Schwartz JB. Clinical pharmacology. In: Hazzard WR, Blass JP, Ettinger, WH Jr, et al., editors. Principles of geriatric medicine gerontology. 4th ed. New York: McGraw-Hill, 1999: 303-31. (Text book)

12. Cockcroft D W, Gault M H. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.

13. Friedman JR, Norman DC, Yoshikawa TT. Correlation of estimated renal function parameters versus 24-hour creatinine clearance in ambulatory elderly. J Am GeriatrSoc 1989; 37:145-49.

14. Liu. Cardiorenal syndrome in heart failure: A cardiologist's perspective. Acute Decompensated Heart Failure. Can J Cardiol 2008 July; 24(Suppl B): 25B-29B.

15. Greenblatt DJ, Allen MD, Shader RI. Toxicity of high-dose flurazepam in the elderly. ClinPharmacolTher 1977; 21: 355-61.

16. Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. Clin PharmacolTher 1997; 61(3): 331-39.

17. Dickstein K, Till AE, Aaarsland T, Tjelta K, Abrahamsen AM, Kristianson K, Gomez HJ, Gregg H, Hichens M. The pharmacokinetics of enalapril in hospitalized patients with congestive heart failure. Br J ClinPharmacol. 1987; 23 (4):403–410.

18. Baughman RA Jr, Arnold S, Benet LZ, Lin ET, Chatterjee K, Williams RL. Altered prazosin pharmacokinetics in congestive heart failure. Eur J ClinPharmacol. 1980; 17 (6):425–428.

19. Crawford MH, Ludden TM, Kennedy GT. Determinants of systemic availability of

hydralazine in congestive heart failure. ClinPharmacolTher. 1985; 38:538–543.

20. Hepner GW, Vesell ES, Tantum KR. Reduced drug elimination in congestive heart failure: Studies using aminopyrine as a model drug. Am J Med. 1978 Aug; 65(2):371-376.