URL: http://dx.doi.org/10.31703/gpsr.2018(III-I).04 Vol. III, No. I (2018) Pages: 27 – 31

Mohammad Faizan Asif [a] Shabana Gulzar Toor [b] Fahad Pervaiz [c]

An Overview of Factors Affecting Renal Clearance

Abstract

Biological Renal clearance comprises multiple active and passive mechanisms, in turn leading to the formation of urine. In this article, a brief review of passive filtration in glomerular capillaries, active tubular secretion, and reabsorption is discussed. Factors affecting renal clearance have also been brought into the discussion, encompassing drug physicochemical properties, drug concentration, the volume of distribution, protein binding, blood flow to kidneys, biological factors, and drug interactions. Further, the necessity of dose adjustment in patients suffering renal impairment has been highlighted.

Key Words: Renal Clearance, Elimination, Excretion, Kidneys, Drugs

Introduction

Most drugs arrive site of activity through the systemic circulation. The blood assists in the transportation of drug particles to respective receptors, for example, in the brain, liver, and kidneys. Contrarily to few drugs being limited to a specific tissue, most drugs are distributed to many tissues depending on the level of selectivity. Commonly tissues serve as repositories, whereas organs such as the liver and kidneys possess the ability to eliminate drugs (Regårdh C. G. 1985).

Basically, elimination comprises biotransformation and discharge of the unaltered medication. The excretion is dominant in the kidneys, yet the bile may also likewise contribute to it. However, the role of bile excretion is more significant in animals (Regårdh C. G. 1985).

Water solubility plays a major role in determining drug elimination through metabolism or excretion. A factor vital in deciding if a medication will be disposed of by digestion or by renal discharge is water solvency (Regårdh C. G. 1985). Extremely hydrophobic substances are biotransformed with the help of enzymes, whereas hydrophilic agents are discharged through the kidneys.

Renal Clearance

Renal clearance is an output of a combination of various filtration and secretion mechanisms, which may or may not involve the expenditure of energy. Values of renal clearance may range between none to as high as blood flow in the kidney. The first case mentioned may involve the entire reabsorption of the previously eliminated drug, ultimately leading to no value of clearance. Whereas the other case suggests no reabsorption in tubules, therefore, giving values of clearance as high as renal blood flow. Drugs like felodipine and prenalterol possess abilities of major clearance rates (Regårdh C. G. 1985).

Various methods for calculating clearance are present. Amongst them, the precise but comparatively complex method is linked upon serial determination of the rate of urine withdrawing and active molecules plasma concentrations (Regårdh C. G. 1985).

Glomerular filtration, tubular secretion with energy expenditure, and tubular reabsorption without energy expenditure are the main mechanisms involved in drug excretion. Alongside the tubular region in the kidney, reabsorption with energy expenditure may also play a weak role in drug excretion. Altogether, these are the processes involved in kidney drug clearance and possessing units of millilitre per minute or liter per hour.

Renal clearance hints regarding the mechanisms involved; for example, clearance values well above Glomerular filtration Rate, hints at the involvement of

[a] Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan
[b] Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan
[c] Associate professor, Department of Pharmaceutics, Faculty of Pharmacy, Islamia University of Bahawalpur, Bahawalpur, Punjab, Pakistan. Email: fahad.pervaiz@iub.edu.pk

tubular secretion, whereas in other cases of lesser or closer values may not rule out tubular secretion because this effect is countered by distal tubule reabsorption.

Glomerular Filtration

More than a quarter of the plasma passing in the kidneys is screened by the water pressure in the capillaries of the glomerulus. Since the pore size isn't large enough, it allows limited particles to pass through, based on size and binding ability with various proteins.

The glomerular filtration rate is judged by various external molecules that are thought to be only filtered through glomerular capillaries, e.g., inulin (Regårdh C. G. 1985). Since using inulin for assessing glomerular filtration rate time taking, therefore, using creatinine is a better alternative.

According to researchers, creatinine has several drawbacks, like it gives over- results in masses possessing greater creatinine concentrations or kidney malfunctioning.

Alternatively, and comparatively novel way for measuring glomerular filtration rate is through Cr-EDTA. Using Cr-EDTA has several benefits over previous, e.g. quicker, accurate, and improved patient compliance. However, drawbacks of using this method include difficulty in day-to-day clinical operations (Regårdh C. G. 1985).

Tubular Secretion

API molecules may become urine through secretion in the tubule region. This mechanism requires energy expenditure to transfer drugs. Contrary to filtration in the glomerular region, it is not affected by protein binding. Several drugs being greatly protein-bound successfully are eliminated.

There exist two methods through which secretion may occur, i.e., method of transporting anionic and cationic molecules. The efficiency of this mechanism is proportional to the blood circulation in the kidneys. Paraaminhuppuric acid is present in plasma and unable to get reabsorbed in the tubular region; therefore, clearance is unable to be calculated directly. Corrective action for hematocrit needs to apply. Various drug molecules possess clearance greater than blood flow in kidneys, which hints that molecules linked with RBC are also withdrawn by the respective mechanism. Contrary, active molecules possessing kidney clearance nearly equivalent to kidney blood flow are uncommon. Various drugs have kidney clearance higher than the filtration rate in the glomerular region indicate the active secretion in the tubular region. Various acidic and basic drugs eliminated by tubular secretion include salicylates, probenecid, Ethambutol, and pindolol. Acidic drugs seem to more profoundly interact with excretion rates, e.g., probenecid, and various penicillins, probenecid and frusemide, probenecid, and methotrexate (Regårdh C. G. 1985).

Reabsorption

Primarily produced urine by filtration process in glomerular capillaries is reabsorbed. Most of the reabsorption takes place in the proximal region of tubules accompanied by the distal region and collecting duct. Consequently, this leads to enhanced concentration of the drug, which was previously glomerular filtered or tubular secreted or both in the urine. The difference in pressure of fluid in tubules and capillaries increases the reabsorption by the process of diffusion. Various elements affecting this process include physicochemical properties (commonly lipophilicity) and constant related to ionization. The pH of urine also has a significant effect on reabsorption.

Several active molecules, which are weak electrolytes, have values varying in pH 5 and 8. The renal excretion of such molecules may get affected by the pH of urine deviations as drugs can be reabsorbed in a non-ionized state. In accordance with the Henderson-Hasselbalch equation, ionization is directly proportional to urine pH for acids whereas inversely proportional for bases. In addition, the Polar and nonpolar nature of drugs also possess significance. This may be evident as kidney excretion of polar atenolol is least dependent on urine pH, whereas the case is vice-versa for unipolar propanolol. The rate of Urine flow also possesses prime importance in determining drug clearance. The formation of urine and the available time for the drug to get reabsorbed may affect the flow of urine (Regårdh C. G. 1985).

Other factors Affecting Renal Clearance

Physicochemical Properties

Physicochemical properties possess a significant role in determining the rate of clearance by kidneys. The molecular weight and size of the drug molecule are amongst the main physicochemical properties. Compounds having a molecular weight of around 300 daltons along with water solubility or hydrophilicity are excreted mainly through kidneys

(Brahmankar, 2005). In contrast, compounds having M.W well above 500 daltons are excreted through bile instead of the renal route.

Another major property includes acid dissociation constant pKa, which indicates the strength of an acid. A greater value of pKa indicates weak acid and vice versa. Without expenditure of energy, a polar and ionized drug is not well absorbed, and ultimately its fate is to get excreted rapidly. A drug that has ionized and lipophilic in nature can be passively reabsorbed. On the other hand, unionized drug polar in nature is easily excreted through the kidney, ultimately in the urine.

Another factor that has an impact on renal clearance is the stereoselective protein binding ability of various drugs (Tocco *et al.* 1990). This is evident from the fact various enantiomers of a specific drug exhibit diverging filtration rates. In most cases, chiral drugs like duloxetine and rosuvastatin attach to various body proteins through this mechanism. Indobufen exhibits in two forms R and S indobufen, respectively. S-enantiomer of this drug with the weaker binding ability to Human serum Albumin, therefore, enhanced drug clearance compared with R- enantiomer of indobufen (Brahmankar, 2005).

Plasma Drug Concentration

Glomerular filtration, along with reabsorption, both are passive processes and are therefore affected by the concentration of active agents directly—a clear, direct relationship between excretion rate and drug concentration. Active agents reabsorbed with the expenditure of energy; the excretion rate is directly proportional to plasma concentration until saturation happens. Whereas drugs that are reabsorbed actively, the rate of excretion is limited at lower concentrations (Brahmankar, 2005). These drugs are eliminated from the body when the concentration in filtered fluid from the glomerulus surpasses the reabsorption capacity.

Distribution and Binding Ability of Drugs

Clearance possess an inverse relation with distribution volume which means an increase in the distribution of drugs leads to decreased renal clearance of drugs and vice versa. Drugs being attached to the protein present in plasma act as large molecules that are unable to cross the pores of smaller size present in glomerular capillary walls. On the other hand, particles of lesser size can easily pass through the glomerular pores and ultimately form primary urine fluid. Equation of renal clearance equals to the product of fraction unbound of the drug in plasma and flow rate of urine (Brahmankar, 2005). This justifies the existence of the direct relationship between unbound drug molecules and renal clearance.

Drugs that are secreted actively through the tubular region are less affected as compared to drugs undergoing filtration without the expenditure of energy. Penicillins are mainly secreted actively (Brahmankar, 2005).

Blood Flow to Kidneys

Amongst the factors that impact kidney clearance rate, blood flow also possesses a vital role. The increased flow of blood through kidneys leads to enhanced active molecules interaction with secretory pores present in glomerulus and tubules and, in turn, enhances the elimination rate (Brahmankar, 2005).

Biological Factors

Biological factors also affect renal clearance amongst the main factors, Personage, gender, racial and genetic background (Brahmankar, 2005). According to studies, females possess a lesser excretion rate when compared with males. Similarly, infants or children have significantly lesser renal functionality as compared to teenagers and mature adults (Brahmankar, 2005). In contrast, in aged people, glomerular filtration and active secretion in tubules are decreased, ultimately leading to reduced renal excretion.

Drug Interactions

Drug interactions interacting and modulating any of the stages of kidney function or urine formation will impact the drug clearance rates. During the interaction of drugs, one drug displaces another, ultimately enhancing the renal clearance.

The interaction of gentamycin and furosemide is well known for altering the clearance rate. Furosemide displaces mentioned antibiotic from protein binding, ultimately resulting in unbound gentamycin and enhanced clearance from the body. Elimination of alkaline active molecules from the body is enhanced upon the increased urine acidity due to acidic drugs. Contrarily, alkaline drugs increase the pH of urine, leading to the elimination of acidic drugs from the human body. Phenylbutazone, a drug commonly prescribed as a pain reliever, competes with acetohexamide, ultimately modulating its action duration. Similarly, diuretics also are involved in the

modulation of kidney clearance rate (Brahmankar, 2005).

Diseased Conditions

Renal malfunctioning mainly results from insulin resistance or diminished production, decrease in blood reaching kidneys, toxicity caused by various active drugs or heavy metals. Uremia, marked by high plasma urea concentration, also impacts renal clearance. In both cases, drug toxicity may result.

Determination of Renal Clearance

Optimum renal functioning can be indicated by its filtration rate in glomerular vessels. There are various molecules or agents which may serve as an indicator of renal functioning. These agents may be endogenous- inside the body or exogenous- introduced from outside the body. Any agent who can completely get discharged in unaltered form from glomerular capillaries accompanied by being non-reactive or inert in nature can be employed as an effective indicator of clearance.

Inulin is exogenous, whereas creatinine is an endogenous compound used for this purpose. A major advantage of creatinine over inulin includes the elimination of urine collection and the ability to measure its creatinine concentration in body fluids. Creatinine clearance measurement formulas are separate for children of age between 1 to 20 years and adults above 20 years of age (Brahmankar, 2005).

Therefore, creatinine serum values determine the functioning of kidney clearance. On average, these values range from 120 to 130 ml/min. Any deviation from these optimum values hints at the malfunctioning of kidneys. Serum creatinine clearance with values high as 50ml min^{-1} and as low as 20 ml min^{-1} indicates a medium kidney malfunctioning. Serious failure is indicated by the value of creatinine lower than 10 ml min^{-1} (Brahmankar, 2005).

Dose Adjustment in Renal Failure

The necessity of dose adjustment for the patient with renal functioning compromised is significant. This is because the drug or active substance is unable to get eliminated from the body timely therefore resulting in increased drug half-life (Brahmankar, 2005). In this case, if the unaltered dose is administered to the patient, it may lead to drug toxicity. For drugs with a narrow therapeutic index, there exist a must need for dose adjustment. Contrarily, drugs considered to possess a wider therapeutic window or index may sometimes not need to get their dose altered in renal compromised patients (Brahmankar, 2005).

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