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PHARMACODYNAMICS AND PHARMACOKINETICS OF DIURETIC AGENTS

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Abstract:
Diuretic agents are commonly prescribed medications in various diseases such as hypertension, congestive heart disease, and several causes of oedema. Different types of diuretics are currently available and, though their somehow closely similar mechanisms of action, their final effect depends primarily on their pharmacokinetic and pharmacodynamic properties. Pharmacokinetics describe delivering the drug to the site of action in certain concentrations and at a certain time, whilst pharmacodynamics implies the final response of the diuretic agent at the active site of response. Understanding the basic pharmacokinetic and pharmacodynamic properties of different diuretics is fundamental for physician to appropriately tailor the diuretic agent to each patient. Therefore, this article aims at reviewing and summarizing the pharmacokinetics and pharmacokinetics of different diuretic agents namely loop diuretics, thiazide diuretics, osmotic diuretics, and potassium sparing diuretics.

Keywords: *Diuretic, pharmacodynamics, pharmacokinetics.*

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INTRODUCTION:

Diuretics are a group of medications commonly prescribed for many medical conditions particularly hypertension, congestive heart disease, renal failure, hepatic failure, increased intracranial tension, and various causes of oedema [1,2]. Diuretics act mainly through modulation of water and sodium reabsorption at the renal tubules and subsequently modulating volume homeostasis and blood pressure [2]. Several types of diuretic agents are available with different mechanisms of action. The main types of diuretics are loop diuretics, thiazide diuretics, carbonic anhydrase inhibitors, osmotic diuretics, and potassium-sparing diuretics such as spironolactone, amiloride, and triamterene [2].

The effect of different diuretics is chiefly determined by their pharmacokinetic and pharmacodynamic properties[3]. Pharmacokinetics describes the factors responsible for delivering the drug to the site of action. Pharmacokinetic properties determine the total concentration of drug reaching the active site of action and the duration required for its delivery. Pharmacodynamics, on the other hand, implies the final response of the diuretic agent which is affected by various factors including renal tubules sensitivity to diuretics, fluid and electrolyte status, and general or systemic diseases. For instance, the pharmacodynamics of diuretics are significantly affected by low sodium and potassium levels in blood [4]. This article aims at reviewing and summarizing the pharmacokinetics and pharmacokinetics of different diuretic agents.

LOOP DIURETICS: PHARMACOKINETICS AND PHARMACODYNAMICS

As their names indicates, loop diuretics act on the ascending limb of loop of Henle of nephrons through modulating the Na^+-K^+-Cl^- co-transporter inhibiting reabsorption of sodium, potassium, and chloride [5]. Furthermore, they stimulate the renin-angiotensin system resulting in increased release of renin. This will subsequently increase the glomerular perfusion and glomerular filtration rate [5]. Furosemide is the prototype of loop diuretics, and other agents include torsemide, bumetanide, and ethacrynate [5].

Loop diuretics are rapidly absorbed through the intestine and they reach a peak plasma level within half to two hours from their intake [3]. Torsemide, bumetanide, and ethacrynate have similar rates of absorption and elimination [6]. Frusemide, in contrast, has a faster elimination than absorption name. This phenomenon is referred to as "absorption-limited kinetics" which manifest clinically as a delayed serum peak of the drug and subsequently a slower onset of action in comparison to other diuretics[6]. The rate of absorption also affects the bioavailability of loop diuretics. Frusemide has a very wide range of bioavailability because of its absorption-limited kinetics. The bioavailability of frusemide ranges from 10% to 100%. Diuretics with fixed absorption rate, such as torsemide and bumetanide, have a high bioavailability ranging from 80% to 100%[6]. Knowledge of the bioavailability of each diuretic is essential for the physician to decide about the dose of the drug to be given via oral and intravenous routes. Diuretics with high bioavailability (such as bumetanide) can be administered in closely similar oral and venous routes[7,8]. In contrast, switching from a venous to oral route of administration of diuretics with lower bioavailability (such as frusemide) require increasing the dose up to twice the venous route to get the same effect [7,8]. After an oral administration, the drug reaches a peak within 1 to 1.5 hours, whilst after venous administration; it reaches a peak within minutes [5].

After absorption, the diuretic agents are distributed to different tissues volumes. The volume of distribution is closely similar among different diuretics. The volume of distribution of bumetanide, frusemide, and torsemide is 0.17, 0.16, and 0.16, respectively[3,5]. The half-lives, on the other hand, are variable. The loop diuretic with the longest half-life is torsemide wherein the drug stays for 3 to 4 hours. Frusemide has a half-life of 90 minutes, and bumetanide has a half-life of about 60 minutes [4].

As regards elimination, about two-thirds of bumetanide and frusemide are excreted in urine unchanged[4]. Torsemide, on the other side, is mainly eliminated through hepatic metabolism (80%) by the action of cytochrome P450 2C9, and only 20% are excreted in urine. Rapid elimination of loop diuretics is beneficial because it allows the nephrons to restore sodium level, a phenomenon known as "Braking" effect [2,3].

At the renal parenchyma, loop diuretics of response cannot be excreted through glomerular filtration[5]. Therefore, an active transport is necessary to move the diuretic agent across the renal tubular membrane to be excreted and act. The higher the concentration of diuretic agent at renal tubules, the higher diuretic response they achieve [5].

The action and response to loop diuretics can be affected by various factors. For instance, diseases with oedematous status – such as hepatic failure, renal failure, and others – reduce the response to loop diuretics in comparison to their counterparts from the

general population [9-14]. Renal impairment significantly affects the pharmacokinetics rather than pharmacodynamics of loop diuretics [13]. Renal impairment results in reduction of diuretics excretion into urine, and competitive inhibition at cellular level for excretion[13,14]. Hepatic failure, on the contrary, does not affect the pharmacokinetics, but has a considerable impact on pharmacodynamics. It increases solute reabsorption at renal tubules and consequently increases their response [15,16].

THIAZIDE DIURETICS

Thiazide diuretics are group of diuretic agents that include in their chemical structure a benzothiazide compound[5]. The most common thiazide diuretics are hydrochlorothiazide, chlorothiazide, chlorothalidone, and indapamide [2,3]. As loop diuretics, thiazide diuretics are also rapidly through the gut reaching a peak serum level within 1.5 to 4 hours from their intake[2]. The half-lives of thiazide diuretics are considerably longer than loop diuretics with some agents reaching a half-life of 55 hours [2]. The reported half-lives of hydrochlorothiazide, chlorothiazide, chlorothalidone, and indapamide are 3-30 hours, 15-27 hours, 25-55 hours, and 15-25 hours, respectively [17].

After absorption, the bioavailability of thiazide diuretics varies. The highest bioavailability is reported among indapamide diuretics (more than 90%), and the lowest is noted among chlorothiazide diuretics (30-50%) [18]. Hydrochlorothiazide and chlorothalidone have an average bioavailability of about 65%[18]. Diuretics act at the nephron at the urinary side rather than the blood side. Therefore, the urinary excretion rate is an important determinant of their potency. Hydrochlorothiazide possess the highest urinary excretion rate with about 40-80% of the drug being excreted unchanged in urine [7,17]. About 65% of chlorothalidone and only 20% of chlorothiazide are excreted in urine [1,2]. Indapamide is excreted in very small quantities in urine (only 2%) and, thus, it is thought that it may be a potent agent acting in this very low concentration or it has an active metabolite that exerts its diuretic effect [1,2].

At the renal tubules, thiazide diuretics act by inhibition of sodium-chloride co-transporter (SLC12A3) at the distal convoluted tubules[19,20]. Under normal physiological condition the sodium-chloride co-transporter re-uptake sodium and chloride ions from the renal tubule lumen back to the blood via an active ATP-dependent sodium-potassium pump[2]. Thiazide prevents this process leading to excretion of sodium, chloride, and water into the renal tubular lumen resulting in diuresis [3,4]. Thiazide diuretics are fairly potent diuretics. Even though, they have minimal effect on serum sodium level disturbance because less than 5% of sodium is excreted at the distal convoluted tubules where thiazide diuretics act [17]. However, thiazide diuretics have their side effects such as hypokalemia and arrythmia[5].

OSMOTIC DIURETICS

Mannitol is the prototype of osmotic diuretics [21,22]. It is commonly prescribed to patients with acute oliguria so as to prevent deleterious consequences such as acute kidney injury[22]. In the worst scenario, using mannitol in these cases would convert the oliguric acute kidney injury into non-oliguric acute kidney injury [22]. Mannitol is also commonly prescribed by neurologists for patients with intracranial hypertension due to intracerebral edema [23].

Mannitol is rapidly acting after intravenous administration, and it has a half-live of about 1 hour in patients with normal renal functions [1,4]. However, the half-life is significantly prolonged in patients with end-stage chronic kidney disease (up to 36 hours) [24]. If the patient is on peritoneal dialysis or hemodialysis, the half-life will get reduced to 21 hours and 6 hours, respectively. The average elimination time of mannitol from the body is 1.5 days. Unlike peritoneal dialysis, hemodialysis fastens mannitol elimination. Therefore, it may be used in cases of excessive unneeded doses of mannitol [24].

Mannitol acts through retaining water in the intravascular space through osmosis [3]. Rapid intravenous administration of mannitol is essential for diuresis[25]. Despite its advantages, mannitol is usually used with caution because of its adverse events. Mannitol may result in precipitation of volume overload, congestive heart failure, or electrolyte disturbance (particularly hyponatremia) [24]. Therefore, caution should be taken during its administration.

POTASSIUM-SPARING DIURETICS

Potassium sparing diuretics are another important type of diuretics. Examples of these diuretics are amiloride, triamterene, and spironolactone[26]. Potassium sparing diuretics act at the distal portion of the distal convoluted renal tubules and the cortical collecting ducts through inhibition of sodium and water reabsorption while preventing potassium from urinary loss [26].

Spironolactone is the prototype of potassium-sparing diuretics. After oral intake, it is metabolized into its

active metabolite "canrenone" in hepatocytes and intestinal cells [27,28]. Canrenone has a long half-life and it is thought to be responsible for the diuretic effect of spironolactone [28]. The spironolactone action, therefore, is delayed beyond 24 hours from oral intake, and the peak actions occur after three to four days [28]. Triamterene and amiloride have a more rapid onset of action. Triamterene has an extensive first pass metabolism at the liver, and it is secreted in the kidney in the form of sulphate ester which is considered its active metabolized. Amiloride, in contrary, is excreted unchanged in urine [26].

At their site of action, potassium-sparing diuretics exert their diuretic effect via variable mechanisms. Spironolactone, for instance, acts by competitive inhibition of aldosterone at the luminal membrane of the distal convoluted tubules and the renal collecting ducts[29]. This results in blocking the upregulation of the ENaC channels and the sodium-potassium-ATPase pump, and consequently leads to antagonizing sodium reabsorption and potassium excretion [29]. Because of its mechanism of action on aldosterone, spironolactone action is significantly reduced in cases of hypoaldosteronism[30]. Triamterene and amiloride, on the other side, act via different mechanisms. They act at the distal convoluted tubules via non-aldosterone dependent mechanisms through blocking sodium reabsorption at the luminal surface of these tubules [24].

CONCLUSION:

Diuretics have different pharmacokinetic and pharmacodynamic properties, and they act by different mechanisms at renal tubules. Osmotic diuretics have the most rapid onset of action after their parenteral administration (minutes), whilst potassium-sparing diuretics have the longest onset of action (more than 24 hours) as they act via an active metabolite. The peak of action of diuretics range from few hours - as in case of loop, thiazide, and osmotic diuretics – to several days – as in case of spironolactone. Loop diuretics act at the loop of Henle, whereas thiazide and potassium-sparing diuretics act at the distal convoluted tubules. Certain co-morbidities may affect the action of certain diuretics. For instance, loop diuretics action is considerably affected in cases of hepatic cirrhosis, congestive heart failure, and chronic kidney disease, and spironolactone action is affected in cases of hypo or hyperaldosteronism. Therefore, understanding the basic pharmacokinetic and pharmacodynamic properties of different diuretics is fundamental for physician to appropriately tailor the diuretic agent to each particular patient.

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REFERENCES:

1. Wile D. Diuretics: A review. *Ann Clin Biochem*. 2012. doi:10.1258/acb.2011.011281
2. Roush GC, Kaur R, Ernst ME. Diuretics: A review and update. *J Cardiovasc Pharmacol Ther*. 2014. doi:10.1177/1074248413497257
3. Rahn KH. Clinical pharmacology of diuretics. *Clin Exp Hypertens*. 1983. doi:10.3109/10641968309048818
4. Brater DC. Update in diuretic therapy: Clinical pharmacology. *Semin Nephrol*. 2011. doi:10.1016/j.semnephrol.2011.09.003
5. Sica DA, Carter B, Cushman W, Hamm L. Thiazide and loop diuretics. *J Clin Hypertens*. 2011. doi:10.1111/j.1751-7176.2011.00512.x
6. Wargo KA, Banta WM. A comprehensive review of the loop diuretics: Should furosemide be first line? *Ann Pharmacother*. 2009. doi:10.1345/aph.1M177
7. Ramasethu J. Pharmacology Review. *Neoreviews*. 2004. doi:10.1542/neo.5-11-e491
8. Pacifici GM. Clinical pharmacology of the loop diuretics furosemide and bumetanide in neonates and infants. *Pediatr Drugs*. 2012. doi:10.2165/11596620-000000000-00000
9. Ellison DH, Felker GM. Diuretic Treatment in Heart Failure. *N Engl J Med*. 2017. doi:10.1056/NEJMra1703100
10. Cox ZL, Lenihan DJ. Loop diuretic resistance in heart failure: Resistance etiology-based strategies to restoring diuretic efficacy. *J Card Fail*. 2014. doi:10.1016/j.cardfail.2014.05.007
11. Oyama MA, Peddle GD, Reynolds CA, Singletary GE. Use of the loop diuretic torsemide in three dogs with advanced heart failure. *J Vet Cardiol*. 2011. doi:10.1016/j.jvc.2011.10.001
12. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. *J Am Soc Nephrol*. 2002.
13. Sica DA. Diuretic use in renal disease. *Nat Rev Nephrol*. 2012. doi:10.1038/nrneph.2011.175
14. Shankar SS, Brater DC. Loop diuretics: from the Na-K-2Cl transporter to clinical use. *Am J Physiol - Ren Physiol*. 2003. doi:10.1152/ajprenal.00119.2002
15. Hoorn EJ, Ellison DH. Diuretic Resistance. *Am J Kidney Dis*. 2017. doi:10.1053/j.ajkd.2016.08.027
16. Qavi AH, Kamal R, Schrier RW. Clinical use of diuretics in heart failure, cirrhosis, and nephrotic syndrome. *Int J Nephrol*. 2015.

doi:10.1155/2015/975934
17. British Hypertension Society. *Thiazide and Thiazide-like Diuretics*.; 2008.
18. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide Versus Chlorthalidone: Evidence Supporting Their Interchangeability. *Hypertension*. 2004. doi:10.1161/01.HYP.0000103632.19915.0E
19. Hughes AD. How do thiazide and thiazide-like diuretics lower blood pressure? *JRAAS - J Renin-Angiotensin-Aldosterone Syst*. 2004. doi:10.3317/jraas.2004.034
20. Wang DJ, Gottlieb SS. Diuretics: Still the mainstay of treatment. *Crit Care Med*. 2008. doi:10.1097/01.CCM.0000296272.68078.6B
21. Kokko JP. Site and mechanism of action of diuretics. *Am J Med*. 1984. doi:10.1016/S0002-9343(84)80003-0
22. Karajala V, Mansour W, Kellum JA. Diuretics in acute kidney injury. *Minerva Anestesiol*. 2009. doi:R02085292 [pii]
23. Okoromah CA, Afolabi BB, Wall EC. Mannitol and other osmotic diuretics as adjuncts for treating cerebral malaria. In: *Cochrane Database of Systematic Reviews*. ; 2011. doi:10.1002/14651858.CD004615.pub3
24. CRAIG BRATER. *Diuretic Pharmacokinetics and Pharmacodynamics*. Indianapolis; 1993.
25. Fandino W. Understanding the physiological changes induced by mannitol: From the theory to the clinical practice in neuroanaesthesia. *J Neuroanaesth Crit Care*. 2017;4(3):138. doi:10.4103/jnacc.jnacc_31_17
26. Tamargo J, Segura J, Ruilope LM. Diuretics in the treatment of hypertension. Part 2: loop diuretics and potassium-sparing agents. *Expert Opin Pharmacother*. 2014. doi:10.1517/14656566.2014.879117
27. Jeunesse E, Woehrle F, Schneider M, Lefebvre HP. Effect of spironolactone on diuresis and urine sodium and potassium excretion in healthy dogs. *J Vet Cardiol*. 2007. doi:10.1016/j.jvc.2007.10.002
28. Gardiner P, Schrode K, Quinlan D, et al. Spronolactone metabolism: Steady-state serum levels of the sulfur-containing metabolites. *J Clin Pharmacol*. 1989. doi:10.1002/j.1552-4604.1989.tb03339.x
29. Armanini D, Sabbadin C, Donà G, Clari G, Bordin L. Aldosterone receptor blockers spironolactone and canrenone: two multivalent drugs. *Expert Opin Pharmacother*. 2014. doi:10.1517/14656566.2014.896901
30. Hood SJ, Taylor KP, Ashby MJ, Brown MJ. The Spironolactone, Amiloride, Losartan, and Thiazide (SALT) double-blind crossover trial in patients with low-renin hypertension and elevated aldosterone-renin ratio. *Circulation*. 2007. doi:10.1161/CIRCULATIONAHA.107.690396