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Chloride and its Clinical Implications in Today's Clinical Practice: Not an Orphan Electrolyte

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Abstract

Though chloride is the predominant extracellular anion, it is mostly seen just as an anion accompanying sodium and hardly receives attention in textbooks. But independent evaluation of serum chloride may unearth several clinical and acid-base disorders. It is used in formulas to estimate serum anion gap, urine anion gap, and strong ion difference (Stewart method). Several critical functions of a cell such as maintenance of cell volume, neutralization of H^+ in lysosomal vesicles, epithelial fluid transport, change in cell membrane potential and ligand-gated transmission in the post-synaptic membrane utilize chloride channels. In addition, chloride forms an integral part of anion exchanger proteins coded by SLC26A gene family. Chloride is an essential component of intravenous fluids used in day-to-day clinical practice. The role and contribution of chloride rich fluids and resulting acidosis in causing inferior outcomes in sepsis, renal vasoconstriction, and acute kidney injury has been debated. Numerous genetic diseases are known to be related with chloride channels and proteins abnormalities. In the following review, I would like to bring much needed attention towards importance of chloride in human physiology. The following hypothetical clinical case will be just a spark for fiery chloride.

Keywords: Hyperchloremia; Hypochloremia; Anion exchanger; Chloride channel

Introduction

Case 1: An 18 years old male was brought to ER in an obtunded state. He had an alcoholic smell on his breath and was hemodynamically stable with a blood pressure (BP) of 110/60 mmHg. His physical examination was unremarkable except for him being drowsy. Preliminary laboratory results were as follows; Serum sodium 139 meq/L, potassium 5 meq/L, bicarbonate 22 meq/L, chloride 87 meq/L and glucose of 90 mg/dL. Blood alcohol level was undetectable and urine microscopy was significant for oxalate crystals. A diagnosis of poisoning with anti-freeze (ethylene glycol) was made.

In this patient most of these laboratory information seems normal however serious acid-base disorder can be easily overlooked if attention is not paid towards the remarkably low chloride value which is suggesting here a complex acid base disorder with high anion gap metabolic acidosis (serum anion gap of 30) and superimposed metabolic alkalosis (delta gap of 18 and delta ratio of 10). The high anion gap pointed towards unmeasured anions which were later found to be oxalic acid, the metabolite of ethylene glycol.

Serum Anion Gap = serum Na^+ – [Cl^- + $HCO3^-$] ---------- (eq.1)

Delta gap= Measured anion gap – Normal anion gap – Normal [$HCO3^-$] – Measured [$HCO3^-$] ---------- (eq.2)

$$\textbf{Delta Ratio} = \frac{\text{Measured anion gap-Normal anion gap}}{\text{Normal } [HCO3^-] - \text{Measured } [HCO3^-]} \text{-------} \quad \text{(eq.3)}$$

Na^+, Cl^- and $HCO3^-$ in meq/L

Chloride is the predominant extracellular anion with normal concentration ranging from 94-111 meq/L [1]. It is commonly ingested as table salt (sodium chloride). In early experiments, it was determined that chloride's total body concentration was 30 meq/Kg body weight and intracellular concentration was 24.8 meq/L of cell water which was 29.7% (range 19.8-40.4%) of total body chloride [2]. Chloride is mostly seen just as an anion accompanying sodium and hardly receives attention in textbooks. But, independent evaluation of serum chloride may unearth several clinical and acid-base disorders. Chloride significantly contributes to plasma tonicity and is used in formulas to estimate serum anion gap, urine anion gap, and strong ion difference (Stewart method) [3] which is less popular for use in clinical practice due to its complex interpretations.

Urine Anion Gap = urine [Na^+ + K^+] – Cl^- ---------- (eq.4)

Strong ion difference = (Na^+ + K^+ + Mg^{++} + Ca^{++}) – (Cl^- + lactate + other strong anions) ---------- (eq.5)

Na^+, K^+, Cl^-, $HCO3^-$ in meq/L

The role of chloride in urine anion gap measurements is unique and indirect as chloride here is serving as a surrogate marker of NH_4^+ excretion in urine. A positive urine anion gap in the presence of metabolic acidosis is often abnormal and points towards low urinary NH_4^+ excretion, thus impaired urinary acid excretion.

Chloride Physiology

During early experiments, hyperchloremia was found to be associated with renal vasoconstriction and fall in glomerular filtration rate that was independent of renal sympathetic nervous activity [4]. Now it is known that functions and physiochemical actions of chloride are mediated via chloride channels (ClC), which participates in several critical functions of a cell such as maintenance of cell volume (volume sensitive ClC), neutralization of H^+ in lysosomal vesicles (ClC3, ClC5, ClC7), epithelial fluid transport (CFTR, ClC-Ka, ClC-Kb), change in cell membrane potential (ClC1, ClC2, calcium-ClC) and ligand gated

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transmission in the post-synaptic membrane (GABA and glycine channels) [5-7]. In the mouse models, function of aquaporin-6 is also shown to involve chloride transport [7]. Macula densa cells perform their crucial function of tubuloglomerular feedback by sensing chloride concentration in tubular fluid [8]. Chloride also forms an integral part of SLC26A anion exchanger protein. Chloride is also an essential component of intravenous fluids used in day-to-day clinical practice and it concentration in different replacement fluids (mmol/L) is as follows [1]:

4% Albumin= 128; Normal saline (0.9%) = 154, Half normal saline (0.45%) = 77, Ringers lactate= 111, PlasmaLyte= 98, Hydroxyethyl starch= range 110-154

Finally, the role and contribution of chloride rich fluids and resulting acidosis in causing inferior outcomes in sepsis [3], renal vasoconstriction [3] and acute kidney injury [9] has been debated [3].

Handling of chloride by the kidneys

Approximately 21000 meq of chloride is filtered everyday of which >99% is absorbed (55% in proximal tubule, 25-35% in thick ascending loop (TAL) of Henle and rest in distal tubule) and only 100-250 meq is excreted every day [10]. Once in proximal tubular lumen, chloride is reabsorbed actively via anion exchanger [SLC26A6] (chloride-formate, chloride-hydroxyl, chloride-oxalate exchanger) on luminal side and leave the cells via K^+Cl^- co-transporter and chloride selective channels [10]. Chloride is also reabsorbed passively across tight junctions in proximal tubule [10]. In the proximal tubule, ClC5 (H^+/Cl^- antiporter) helps to secretes H^+ into endosomes and maintain low pH that is necessary for protein degradation [5-7].

In TAL, chloride is reabsorbed via luminal Na-K-2Cl cotransporter and leaves the cell via ClC-Ka channel co-localized with Barttin protein. Furosemide that is a loop diuretic, works on TAL via competing for binding to chloride site on the Na-K-2Cl cotransporter. Reabsorption of sodium chloride in TAL is essential for generation of medullary osmotic gradient, a pre-requisite for excreting concentrated urine.

Once tubular fluid reaches macula densa, its activity is modulated by chloride concentration such that low chloride concentration activates macula densa cells and thereby stimulates renin release. In distal convoluted tubule, chloride is actively reabsorbed via luminal Na-Cl cotransporter and leaves the cell via basolateral chloride channel [11]. Chloride may be absorbed by paracellular route as well. WNKs (with no lysine [K]) are the unique serine/threonine kinases and recently known to regulate activity of Na-Cl cotransporter in distal tubule. Thiazide diuretics which work in distal tubule acts by blocking Na-Cl cotransporter activity.

In the collecting tubule, principal cell absorbs sodium via epithelial sodium channel (ENaC) and creates electronegative lumen that stimulates paracellular chloride reabsorption, which if increased significantly, may impair potassium and proton secretion due to loss of electrochemical gradient. Type A intercalated cell has basolateral Cl^--HCO_3^- exchanger (SLC4A1) which extrudes HCO_3^- outside the cell in exchange for in-coming chloride ion, whereas type B intercalated cell has Cl^--HCO_3^- exchanger (SLC26A4) [3,6] also known as Pendrin, located at luminal side which secretes HCO_3^- into the tubular lumen in exchange for chloride [11]. These are the crucial transporters involved in distal tubular proton excretion.

Beside kidneys, ClC-Ka and CLC-Kb in the stria vascularis in the inner ear are involved in chloride recycling and their mutation leads to congenital deafness [5,6]. Also, Cl^--HCO_3^- exchanger (band-3 or anion exchanger-1) plays crucial role in red blood cells in maintaining electro-neutrality [11]. Another unique chloride channel is cystic fibrosis transmembrane conductance regulator (CFTR) that is a located in apical membrane of epithelia and involved in transepithelial salt transport, fluid flow, and ion concentration [12]. Parchorin is a recently discovered intracellular chloride channel in water secreting cells such as salivary glands, lachrymal glands, pancreas, cochlea and kidneys whereby it plays a critical role in water secretion by regulation of chloride transport. Prestin is another SLC25A5 gene encoded chloride/bicarbonate anion exchanger protein and present on outer hair cells of cochlea [13].

Causes of chloride disorders

Hypochloremia: Low serum chloride is often associated with metabolic alkalosis that could be due to volume loss from gastric content as gastric fluid is rich in chloride (Cl^-) along with proton (H^+) both of which together forms hydrochloric acid [3] or from kidneys such as due to diuretics or salt wasting nephropathies (Bartter and Gitelman Syndrome) [14].

In these cases, chloride depletion also plays a crucial role in maintaining metabolic alkalosis. Decreased delivery of chloride to the macula densa stimulates renin release which activates angiotensin and aldosterone and thereby promotes proton excretion in the distal tubule. The lower chloride concentration in the tubular lumen also impairs activity of luminal Cl^--HCO_3^- exchanger in type B intercalated cell and leads to reduced excretion of HCO_3^-, exacerbating metabolic alkalosis further.

Hypochloremia and metabolic alkalosis may be associated with volume overload conditions such as edema, congestive heart failure, nephrotic syndrome and mineralocorticoid excess [14]. Finally, hypochloremia also often accompanies hyponatremia [3]. Additionally, a case series of 3 patients has been reported whereby hypochloremia and hyponatremia was the initial presentation of cystic fibrosis [15].

As seen in case 1, hypochloremia in the presence of seemingly normal other electrolytes points towards complex acid base disorders such as high anion gap metabolic acidosis and superimposed metabolic alkalosis.

Hyperchloremia: Serum chloride level is usually elevated in inorganic metabolic acidosis and signifies normal-anion gap metabolic acidosis (NAGMA). Differential of NAGMA often includes an inability of the kidneys to excrete an acid load into the urine (renal tubular acidosis) or gastrointestinal loss of bicarbonate due to diarrhea, ureteroenteric fistula or pancreato-duodenal fistula, which can be easily differentiated measuring urine anion gap (eq. 4) which is positive in renal tubular acidosis due to impaired $NH4^+$ excretion. Other causes of NAGMA may include hyper-alimentation, intravenous infusion of chloride rich fluid such as 0.9% normal saline, medications such as carbonic anhydrase inhibitors, ENaC blockers (triamterene, amiloride) or poisoning with toluene, isopropyl alcohol, and salicylates.

Hypernatremia due to dehydration or diabetes insipidus is also often accompanied with elevated chloride level [3]. Spuriously elevated chloride level may be seen in toxicity with salicylic acid [16] and bromide [17] to the extent that the anion gap may be erroneously reported to have a greatly negative value.

Genetic diseases associated with chloride channels and exchangers: Numerous genetic diseases as mentioned briefly below are known to be related with chloride channels and proteins abnormalities.

Bartter Syndrome: It is a salt wasting nephropathy and an autosomal recessive disorder. It is characterized by hypokalemia, metabolic alkalosis, hypochloremia, polyuria and hypercalciuria. Bartter syndrome type I that commonly presents during early life, is due to mutations in SLC12A1 gene that leads to defective Na-K-2Cl cotransporter. Bartter syndrome type III has mutation in CLCNKB gene and ClC-Kb channel [6,7]. Bartter syndrome Type IV has mutation in Barttin which is a β-subunit of ClC-Ka and ClC-Kb channels which is also associated with sensorineural deafness (Bartter with sensorineural deafness). Bartter syndrome type II is caused by mutation in luminal potassium channel, ROMK (renal outer medullary potassium). It leads to impaired recycling of cellular potassium into the tubular lumen, thus inhibiting luminal Na-K-2Cl cotransporter [18].

Gitelman Syndrome: It is also a salt wasting nephropathy, but milder form as compared to Bartter syndrome and is an autosomal recessive disorder caused by mutation in SLC12A3 gene and distal tubular Na-Cl cotransporter. It is also characterized by hypokalemia, metabolic alkalosis, hypochloremia, polyuria, but hypocalciuria and tends to present later in life [18].

Gordon Syndrome: Also known as familial hyperkalemic hypertension or pseudohypoaldosteronism type 2, it has activating mutation in WNK 1 and inactivating mutation in WKN4 (autosomal dominant) protein that leads to over activity of distal tubular luminal Na-Cl cotransporter activity. It is clinically characterized by severe form of low renin and low aldosterone hypertension, hyperkalemia, and hyperchloremic metabolic acidosis [19].

Dent disease: It is an X-linked recessive disorder due to inactivating mutation in ClC5 channel (H^+Cl^- antiporter) [5-7] which causes impaired protein degradation in the proximal tubule and leads to proximal tubular dysfunction, hypercalciuria, proteinuria, rickets or osteomalacia, nephrocalcinosis and chronic kidney disease [5].

Osteopetrosis: Also known as Marble Bone Disease, it has mutation in CLC7 in osteoclasts endosomes and leads to disease due to inability to maintain low pH intracellularly [5]. It can have heterogeneous presentation and involve growth disorder, bone, hematopoietic and neurological abnormalities [20].

Polycystic kidney disease: PCKD is an autosomal dominant disease that is caused by mutation in PKD1 and PKD 2 gene and may mediate via c-AMP dependent chloride secretion in to cysts [7]. It is clinically characterized by development of multiple cysts in each kidney and chronic kidney disease and other extra-renal manifestations such as arterial aneurysms and extra-renal cysts.

Renal tubular acidosis (distal): It is predominantly an autosomal dominant mutation in AE1 gene and basolateral anion exchanger Cl^--HCO_3^- in the distal tubule. Some autosomal recessive forms are also described and rare association with hemolytic anemia is also noted. It is clinically characterized by impaired urinary acidification, non-anion gap hyperchloremic metabolic acidosis, hypokalemia, hypercalciuria, nephrocalcinosis, nephrolithiasis, bone demineralization, and growth retardation [21].

Pendred syndrome: It is an autosomal recessive involving mutation in Pendrin (SLC26A4/PDS gene) and clinically characterized by bilateral sensorineural hearing loss and goiter. Pendrin is an anion exchanger antiporter protein and function as iodide/chloride exchanger in thyroid follicular cells, whereby it help in secreting iodide in colloids, a necessary step for synthesis of thyroid hormones. Pendrin is also expressed in in the inner ear and plays crucial role in homeostasis of endolymph, the fluid bathing neurosensory hair cells [22].

Cystic Fibrosis: It is an autosomal recessive disorder due to mutation in CFTR [5,6,12], a unique chloride channel and clinically characterized by growth impairment, infertility, pancreatic insufficiency, recurrent lung infections, elevated concentration of chloride in sweat and malabsorption.

Since chloride forms an integral part of anion exchanger proteins coded by SLC26 gene, various other genetic diseases in association with abnormal chloride exchangers have been identified. These include diastrophic dysplasia (mutations in the SLC26A2 gene), congenital chloride diarrhea (mutations in the SLC26A3 gene) and deafness (mutations in the SLC26A5 (prestin) gene) [23].

Clinical Approach

Symptoms related to derangement in chloride level usually depend upon underlying cause and hence treatment also widely varies.

Hypochloremia: The initial diagnostic step in patients with hypochloremia and metabolic alkalosis is to assess urinary chloride which if <20 meq/L suggest hypovolemia and also known as chloride-sensitive metabolic alkalosis. Patients promptly respond to volume replacement with normal saline and correction of the underlying etiology such as cessation of diuretics, nasogastric suction, or vomiting.

If urine chloride is >40 meq/L (chloride resistant metabolic alkalosis) it suggests either salt wasting nephropathy such as Bartter or Gitelman syndrome which can be distinguished by urinary calcium excretion or volume overload states such as congestive heart failure, hyperaldosteronism or apparent mineralocorticoid excess which can be differentiated with clinical history, physical exam, echocardiogram and measurement of serum aldosterone level along with plasma renin activity or concentration.

In a patient with hypochloremia with normonatremia and normal or low serum bicarbonate, serum anion gap (eq. 1) and delta gap (eq. 2) or delta ratio (eq. 3) should be routinely measured which will uncover the mixed acid base disorders as seen in case 1. If poisoning with alcohols is suspected, serum osmolar gap (eq. 6,7) also should be calculated. However, in patients with hypochloremia and hyponatremia, the primary focus should be shifted towards hyponatremia management.

Serum Osmolar Gap = Calculated Serum Osmolarity – measured serum osmolarity ---------- (eq.6)

Calculated Serum Osmolarity (mosm/kg) = 2 [Na^+] + BUN/2.8 + Glucose/18 + Ethanol/4.6 ---------- (eq. 7)

Na^+ *(meq/L), BUN, glucose and ethanol (mg/dL)*

Hyperchloremia: It is characterized by high concentration of serum chloride. In all patients, serum anion gap (eq. 1) and delta gap (eq. 2) or delta ratio (eq. 3) should be routinely calculated. If poisoning with toluene is suspected, urine osmolar gap (eq. 8,9) also should be calculated. In the patients with greatly elevated chloride level and negative serum anion gap, toxicity with salicylate or bromide should be suspected and their level should be checked [16,17]

Urine Osmolar Gap = Calculated Urine osmolarity – measured urine osmolarity ---------- (eq. 8)

Calculated Urine Osmolarity (mosm/kg) = 2 [Na^++K^+] + BUN/2.8 + Glucose/18 ---------- (eq. 9)

Na^+, K^+ *(meq/L), BUN & glucose (mg/dL)*

In patients with hyperchloremia and metabolic acidosis, patients usually have normal-anion gap metabolic acidosis that could be either due to gastrointestinal losses or renal loss of HCO_3^- or renal inability to acidify urine. This can be differentiated using urine anion gap (eq. 4) and urine osmolar gap (eq. 8,9).

Conclusion

Disorders of chloride may present in isolation or along with other electrolyte abnormalities. Either way, it has great clinical significance in day-to-day practice. Complex acid base disorders and pathophysiology of a clinical presentation can be missed if enough attention is not towards chloride concentration. Knowledge and research on chloride channels has unraveled numerous genetic diseases. Now, it's time for chloride to receive much needed attention and not be left alone as an orphan electrolyte.

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