Product Monograph

Potassium Chloride Injection,
10 mEq/50mL, 20 mEq/50mL
10 mEq/100mL, 20 mEq/100mL
30 mEq/ 100mL, 40mEq/ 100mL

Electrolyte Replenisher

Manufactured by and distributed by:
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Electrolyte Replenisher

Clinical Pharmacology

Potassium is the major cation of intracellular fluid and is essential for maintenance of acid-base balance, isotonicity, and electrodynamic characteristics of the cell. Potassium is an important activator in many enzymatic reactions and is essential to a number of physiologic processes including transmission of nerve impulses; contraction of cardiac, smooth, and skeletal muscles; gastric secretion; renal function; tissue synthesis; and carbohydrate metabolism[1]. Chloride, the major extracellular anion, closely follows the metabolism of sodium, and changes in the acid-base of the body are reflected by changes in the chloride concentration.

Potassium first enters the extracellular fluid and is then actively transported into the cells. In healthy adults, serum potassium concentrations generally range from 3.5-5 mEq/L. Serum potassium concentrations, however, are not necessarily accurate indications of cellular potassium concentrations, as intracellular potassium accounts for 98% of total body amount. Potassium is excreted mainly by the kidneys. Normally about 80-90% of the potassium intake is excreted in the urine, the remainder in the stools and to a small extent, in the perspiration[2].

Potassium depletion may occur whenever the rate of loss exceeds the rate of intake. Causes of hypokalemia include: inadequate intake, diuretic therapy, diabetic ketoacidosis, metabolic alkalosis, potassium-losing nephropathy, severe diarrhea, prolonged vomiting, drainage of gastrointestinal fluids, hyperaldosteronism, hepatic cirrhosis with ascites, Bartter's syndrome and long-term corticosteroid therapy. Potassium deficiency may cause vomiting, abdominal distention, malaise, myalgia, paralytic ileus, acute muscular weakness, paralysis, paresthesia, polydipsia and an inability to concentrate urine, cardiac arrhythmias, and coma[3]. Hypokalemia may also increase the toxicity of digoxin[4]. Severe potassium depletion (<2.5 mEq/L) may result in elevation of serum creatinine phosphokinase, aldolase, and aspartate aminotransferase levels. Rhabdomyolysis may ensue when the serum potassium concentration falls below 2.0 mEq/L.

Chronic potassium depletion can lead to decreased glomerular filtration rate, renal blood flow, disturbance in tubular sodium handling, impairment of the urinary concentrating ability with polydipsia, and ADH-resistant nephrogenic diabetes insipidus. Reversible pathologic changes include renal hypertrophy and epithelial vacuolization of the proximal convoluted tubule. However, interstitial scarring and tubular atrophy have been reported with prolonged potassium depletion[5].

Indications and Clinical Use

Potassium Chloride Injection is indicated in the treatment of potassium deficiency states where hypokalemia is severe[6,7,8]. Severe hypokalemia is defined as a serum potassium concentration of less than 2.5 mEq/L; serum potassium less than 3.0 mEq/L with definite symptoms or ECG signs of hypokalemia; or serum potassium less than 3.2 mEq/L in the presence of metabolic acidosis and treatment with sodium bicarbonate or insulin is imminent[5].

Potassium Chloride Injection is also indicated in the treatment of hypokalemia ($K+ < 3.5$ mEq/L) in postoperative cardiothoracic surgical patients, where a serum potassium concentration of 4.0 to 5.0 mEq/L is necessary to minimize ventricular arrhythmias[9].

This highly concentrated, ready-to-use potassium chloride injection is intended for the rapid correction of hypokalemia and for potassium supplementation in fluid restricted patients who cannot accommodate additional volumes of fluid associated with potassium solutions of lower concentration [10, 11].

Potassium chloride may be used cautiously to abolish arrhythmias of cardiac glycoside toxicity precipitated by a loss of potassium. This regimen should not be used in patients with atrioventricular block[1].

Contraindications

In hyperkalemia; renal impairment with oliguria, anuria or azotemia; untreated Addison's disease; ventricular fibrillation; salt-losing adrenal hyperplasia; in extensive tissue breakdown as in severe burns, acute dehydration and heat cramps; increased sensitivity to potassium administration (e.g., in congenital paramyotonia or adynamia episodica hereditaria) and hyperadrenalism associated with adrenogential syndrome[3]. Digitalis-induced second- or third-degree heart block is the only type of dysrhythmia in which potassium is contraindicated[4].

Warnings

KCl Injection Concentrate should only be used in an ICU/CCU setting where a detailed protocol for administration of concentrated KCl has been established. Uncontrolled infusion may lead to hyperkalemia.

In patients with impaired mechanisms for excreting potassium, administration of potassium chloride can produce hyperkalemia and cardiac arrest. This is of particular concern in patients given i.v. potassium. Potentially fatal hyperkalemia can develop rapidly and may be asymptomatic. To avoid potassium intoxication, do not infuse these solutions rapidly[3]. Patients must be kept on continuous cardiac monitoring and undergo frequent testing for serum potassium and acid-base balance, especially if they receive digitalis.

Administer intravenously only with a calibrated infusion device at a slow controlled rate (see Dosage and Administration). Administration via a central route is recommended for dilution by the blood stream and avoidance of extravasation[2].

Use in Pregnancy: Animal reproduction studies have not been conducted with potassium chloride. It is also not known whether potassium chloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Potassium chloride should be given to a pregnant woman only if clearly needed [2]. See **Precautions.**

Precautions

Patients with Special Diseases and Conditions: Treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease or acidosis, requires careful attention to acid base balance and appropriate monitoring of serum electrolytes, the ECG and the patient's clinical status.

Use of potassium salts in patients with chronic renal disease, adrenal insufficiency or any other condition which impairs potassium excretion, requires particularly appropriate dosage adjustment.

Use potassium with caution in disease associated with heart block since increased serum potassium may increase the degree of block[3].

Drug Interactions: Extreme caution is advised with concomitant administration of potassium and potassium-sparing diuretics or angiotensin converting enzyme (ACE) inhibitors since the simultaneous administration of these agents can produce severe hyperkalemia.

Laboratory Tests: Serum potassium levels are not necessarily indicative of tissue potassium levels. Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation.

Adverse Reactions

Potassium intoxication with mild or severe hyperkalemia has been reported. The signs and symptoms of intoxication include paresthesia of the extremities, areflexia, muscular or respiratory paralysis, mental confusion, weakness and heaviness of the legs, hypotension, cardiac arrhythmia, heart block, electrographic abnormalities and cardiac arrest. Hyperkalemia may exhibit the following ECG abnormalities: peaked T waves and a shortened QT intervals when serum potassium exceeds 5.5 to 6.0 mEq/L; loss of P waves, widening of the QRS complex, and eventual asystole occurs with higher elevations[5]. Nausea, vomiting, abdominal pain and diarrhea have been reported with the use of potassium-containing solutions[1].

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures.

Pain associated with peripheral infusion of Potassium chloride solution has been reported.

Symptoms and Treatment of Overdosage

Overdose: Symptoms: If excretory mechanisms are impaired or if potassium is administered too rapidly i.v., potentially fatal hyperkalemia can result. Paresthesia of the extremities, listlessness, mental confusion, gastrointestinal symptoms, weakness, heaviness of legs, paralysis, hypotension, cardiac arrhythmias, heart block and cardiac arrest may occur. Frequently, hyperkalemia is

asymptomatic and may be manifested only by increased serum potassium concentration and characteristic electrocardiographic changes.

Progressive ECG changes occur with increasing potassium levels: peaking of T waves, loss of P waves, depression of S-T segment, and prolongation of the QT interval. Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

Treatment: In the event of hyperkalemia, discontinue potassium i.v. administration immediately and institute corrective therapy to reduce serum potassium levels as necessary. The serum potassium concentration and ECG must be monitored, as well as serum electrolytes, creatinine, glucose and arterial blood gases.

Treatment of mild to severe hyperkalemia with signs and symptoms of potassium intoxication includes the following:
1. Elimination of potassium-rich foods, medications and i.v. solutions containing potassium, or medication which can induce hyperkalemia.
2. Dextrose Injection, USP, 10% or 25%, containing 10 units of crystalline insulin per 20 grams of dextrose administered intravenously, 300 to 500 mL per hour.
3. Correction of acidosis, if present, with 40-160 mEq of i.v. sodium bicarbonate infused over 5 minutes. This dose may be repeated after 10-15 minutes if ECG abnormalities persist.
4. Absorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally and as retention enema.
5. Use of hemodialysis or peritoneal dialysis.
6. Use of Calcium gluconate. I.V. calcium is not recommended in patients receiving digoxin.

In treating hyperkalemia in digitalized patients, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity[1,2,4].

Dosage and Administration

The dose and rate of administration are dependent upon the specific condition of each patient.

Administer intravenously only with a calibrated infusion device at a slow, controlled rate. Because pain associated with peripheral infusion of Potassium Chloride solution has been reported, administration via a central route is recommended for thorough dilution by the blood stream and avoidance of extravasation.

Recommended administration rates should not usually exceed 10 mEq/hour or 200 mEq for a 24 hour period if the serum potassium level is greater than 2.5 mEq/L.

In urgent cases where the serum potassium level is less than 2.0 mEq/L or where severe hypokalemia is a threat, (serum potassium level less than 2.0 mEq/L and ECG changes and/or muscle paralysis) rates up to 40 mEq/hour or 400 mEq over a 24 hour period can be administered very carefully when guided by continuous monitoring of the ECG and frequent serum K+ determinations to avoid hyperkalemia and cardiac arrest.

Parenteral drug products should be inspected visually for particulate matter and discolouration, whenever solution and container permit. Use of a final filter is recommended during administration of all parenteral solutions where possible. Do not add supplementary medication[2].

Pharmaceutical Information

Drug Substance
Potassium Chloride, USP
Common/Chemical Name: Potassium Chloride
Molecular Formula: KCl
Molecular Weight: 74.55
Description : Potassium Chloride USP is a white crystalline powder having a melting point of 770 °C. It is freely soluble in water with a pH range of 4.0-8.0 at 25 °C.

Composition
The Potassium Chloride Injection, is a sterile solution of Potassium Chloride, USP in Water of Injection, USP in ready to use single dose container for intravenous admistration. It contains no antimicrobial agents. The composition of various concentrations of Potassium Chloride Injection is as follows :

Pot. Chloride Inj. mEq. **K+**/Container	PotassiumChloride,USP	Water for Injection,USP
10 mEq/50mL	0.746 g	q.s to 50 mL
10 mEq/100mL	0.746 g	q.s. to 100 mL
20 mEq/50mL	1.49 g	q.s. to 50 mL
20 mEq/100mL	1.49 g	q.s. to 100 mL
30 mEq/100mL	2.24 g	q.s. to 100 mL
40 mEq/100mL	2.98 g	q.s. to 100 mL

Stability and Storage Recommendations
The highly concentrated Potassium Chloride Injection is stored in a ready to use plastic container at room temperature (15°C-25°C) . The Viaflex® Plus plastic container is fabricated from a specially formulated polyvinyl chloride. Exposure to temperatures above 25°C during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that these minor losses will lead to clinically significant changes within the expiration period. The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container may leach out certain of its chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials.

Availability of Dosage Forms

The Potassium Chloride Injection, is a sterile, nonpyrogenic, ready to use solution of Potassium Chloride, USP in Water for Injection,USP in a single dose Viaflex® Plus plastic (polyvinyl chloride) container in the following sizes and concentrations.

Product Code No.	**Pot. Chloride Inj. mEq. K^+/Container**	**KCl Concentration**
JB0821	10 mEq/50mL	200 mEq/L
JB0826	10 mEq/100mL	100 mEq/L

JB0822	20 mEq/50mL	400 mEq/L
JB0827	20 mEq/100mL	200 mEq/L
JB0823	30 mEq/100mL	300 mEq/L
JB0824	40 mEq/100mL	400 mEq/L

Pharmacology

Potassium is the major cation of intracellular fluid and is essential for maintenance of acid-base balance, isotonicity and electrodynamic characteristics of the cell. Potassium is also essential in the physiological processes including nerve impulse transmission; contraction of cardiac, smooth and skeletal muscles; gastric secretion; renal function; tissue synthesis; and carbohydrate metabolism. In addition, potassium is an important activator in many enzymatic reactions[1]. Chloride is the major extracellular anion which is essential for the maintenance of acid-base balance.

Pharmacodynamics

In vivo studies performed were designed to evaluate the pharmacodynamics of concentrated potassium chloride administration to critically ill patients, pediatric cardiac surgical patients and cardiopulmonary bypass patients. According to Kruse and Carlson (1990), a positive correlation between the change in serum potassium level and the total dose administered was shown; however, there was only a modest linear correlation between differing hourly rates of potassium administration and change in serum potassium. An average increase in serum potassium level of 0.25 mmol/L per 20 mEq infusion was observed. There was not a clear relationship between changes in potassium and serum creatinine level [7].

The dose-response curve observed by Schaber et al. had a very low coefficient of determination. Eighty-seven percent of responses were an increase in serum potassium. The variability in response to a given dose was expected due to the complex interaction of the physiologic variables involved such as: the dose administered, arterial pH, pre-infusion serum potassium concentration, and serum bicarbonate concentration. A preinfusion serum potassium less than or equal to 3.5 mEq/L was associated with a change in serum potassium of 0.79 $\pm$ 0.23 mEq/kg. Patients with a preinfusion serum potassium less than 3.5 mEq/L received a slightly greater potassium dose than those with a higher preinfusion serum concentration. If the preinfusion serum potassium was greater than 3.5 mEq/L, the change in serum potassium was 0.51 $\pm$ 0.48 mEq/L[11].

Manning et al. (1982) observed that there was only a modest linear correlation between differing hourly rates of potassium administration and change in serum potassium. The mean change in serum potassium after 33.0 mmol of potassium chloride was 0.40 $\pm$ 0.42 mmol/L[9].

Dose Response Data

Study Author	**Pre-infusion Serum [K+]**	**Mean Change in Serum Potassium**
Kruse and Carlson, 1990	3.22 mmol/L	0.25 mmol/L for each 20 mEq administered
Manning et al. 1982	3.6 $\pm$ 0.28 mmol/L	0.40 $\pm$ 0.45 mmol/L after administration of 33.0 mEq

Schaber et al. 1985	$\leq$ 3.5 mEq/L	0.79 $\pm$ 0.44 mEq/L after administration of 0.78 $\pm$ 0.27 mEq/kg
	$\geq$ 3.5 mEq/L	0.51 $\pm$ 0.48 mmol/L after administration of 0.69 $\pm$ 0.19 mEq/kg

Pharmacokinetics

Distribution
Potassium first enters the extracellular fluid and is then actively transported into the cells where its concentration is up to 40 times that outside the cell. According to Kruse et al. (1994), the kinetic behaviour of potassium demonstrated a maximum plasma concentration at the end of the infusion. This maximum concentration decreased rapidly postinfusion and stabilized.

Manning et al. (1982) reported no significant or consistent changes that would indicate a distribution phase.

Elimination
Potassium is excreted mainly by the kidneys. The cation is filtered by the glomeruli, reabsorbed in the proximal tubule, and secreted in the distal tubule, the site of sodium-potassium exchange. Tubular secretion of potassium is also influenced by chloride ion concentration, hydrogen ion exchange, acid-base equilibrium, and adrenal hormones. Surgery and/or tissue injury result in increased urinary excretion of potassium which may continue for several days. Small amounts of potassium may be excreted via the skin and intestinal tract, but most of the potassium excreted into the intestine is later reabsorbed.

Manning et al. (1982) reported that in postoperative cardiopulmonary bypass patients who were administered intermittent concentrated potassium chloride, a mean potassium intake of 37.4 $\pm$ 4.7 mmols resulted in a mean urine potassium excretion of 29.4 $\pm$ 19mmols.

Toxicology
The potential toxic side effects of potassium chloride have been characterized through extensive clinical use for many years. Potassium chloride is a well-characterized drug. The medical literature documents the use of concentrated potassium chloride injection and no occurrence of unusual side effects has been noted when proper administration procedures are followed.

References

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