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Bogotá D.C., 12 de junio de 2018

Señores
DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Ciudad

REFERENCIA: Expediente No. NC2018/0000768
TÍTULO: “ADMINISTRACIÓN INTRAVENOSA DE CITRULINA DURANTE LA CIRUGÍA”
SOLICITANTE: VANDERBILT UNIVERSITY
TRÁMITE: Respuesta al Examen de Forma notificado mediante Oficio No. 1402 del 13 de febrero de 2018.

JAIME EDUARDO DELGADO VILLEGAS, en mi condición de apoderado de la sociedad **VANDERBILT UNIVERSITY**, dentro del término legal, presento respuesta al Examen de Forma notificado mediante Oficio No. 1402 del 13 de febrero de 2018.

1. PODER (Art. 26 D 486, literal f)

El Examinador require:

“Debe allegar el poder otorgado al abogado Jaime Eduardo Delgado que aparece en la solicitud como apoderado”

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R/: De acuerdo a la solicitud del Examinador, me permito adjuntar el Poder otorgado por el Dr. Janis Elsner quien como representante Legal de la sociedad VANDERBILT UNIVERSITY me faculta para tramitar la patente enunciada en la referencia.

2. RESUMEN (Art. 26 literal e) y 31 D486)

El Examinador señala:

“La solicitud no presenta el Resumen por lo que debe allegarlo de conformidad con lo dispuesto en el artículo 31 D. 486. El cual establece que el resumen consiste en una síntesis de la divulgación técnica contenida en la solicitud de patente de invención, debe adecuarse el resumen a lo dispuesto en dicha norma, teniendo en cuenta que el extracto permitirá precisar el objeto de la invención, sus elementos característicos y el campo de aplicación”.

R/: El solicitante se permite presentar el Resumen de la Invención, como sigue:

“La presente invención provee una composición médica, la cual comprende dos componentes: (a) un fluido de reemplazo de hemoconcentración y (b) citrulina; y métodos para preparar esta composición combinando los dos componentes. La composición resultante se puede usar en cirugía cardíaca para mejorar los resultados quirúrgicos”.

3. DESCRIPCIÓN (Art. 28 D486)

El Examinador objetó la descripción de la invención porque:

“La descripción no divulga la invención de manera suficientemente completa para que una persona normalmente versada pueda ejecutarla o reproducirla, considerando que el capítulo reivindicatorio reclama “una composición que consta de citrulina”, pero el capítulo descriptivo no muestra el desarrollo de tal composición. La descripción propiamente dicha de la estructura de la invención, debe ser redactada con suficiente detalle como para que pueda ser realizada por alguien ajeno al solicitante”.

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R/: El solicitante se permite aclarar que, la estructura química de la citrulina es bien conocida en la técnica. En la descripción de la Invención, se describe que la Citrulina (ácido 2-amino-5- (carbamoilamino) pentanoico) [C₆H₁₃N₃O₃] es un aminoácido. La solución de citrulina para administración intravenosa se puede fabricar por métodos conocidos en la técnica, tal como se puede ver en la descripción de la invención, por ejemplo, página 32, renglones 17 a 24, se menciona las formulaciones de citrulina, Kakimoto, et al. (1971) Appl Microbiol 22 (6): 992 - 999; así como, en las páginas 32 renglones 26 a 32 a página 36 renglones 1 a 14 donde se describen formulaciones y cantidades para preparar las composiciones reivindicadas por métodos conocidos por los expertos en la técnica; además en el documento Aucella et al. Lesión Renal Aguda (2007) 156: 287-296, ver **Anexo I**.

4. REIVINDICACIONES RELATIVAS A UN USO (Art 14 D 486)

El Examinador objetó las reivindicaciones de la invención porque:

"Las reivindicaciones 8, 15 y 16 no son patentables de acuerdo con el Art. 14 porque reclaman el "uso durante la cirugía cardíaca", "el uso de citrulina en la fabricación" y "uso durante cirugía para un defecto cardíaco", respectivamente. A diferencia de un producto o procedimiento, un uso no es patentable toda vez que no es susceptible de aplicación industrial".

R/: El solicitante **modificó la Reivindicación 8** donde se **eliminó la mención de un "uso"**, ya que este elemento hace que la reivindicación presuntamente carezca de aplicación industrial.

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Las **reivindicaciones 15 y 16** se han **eliminado**.

5. EXCEPCIÓN DE LA PATENTABILIDAD (Art 20 D 486 literales (a) – (d))

El Examinador objetó las Reivindicaciones 2, 5, 9 y 12 porque: no son patentables de acuerdo con el literal d) del Art. 20, toda vez que reclaman métodos de tratamiento cuando se refieren a que "la composición se formula para su administración al paciente" o "se formula para administrarse perioperatoriamente".

R/: El solicitante se permite manifestar que las **Reivindicaciones 2, 7, 12 y 14 a 16 han sido eliminadas**.

Las **Reivindicaciones 5 y 9** indican que la composición está formulada para la administración durante el bypass cardiopulmonar.

5. REIVINDICACIONES (Art 30 D 486)

El Examinador objeto el capítulo reivindicatorio porque:

"La reivindicación 1 no es clara porque describe el objeto de la solicitud en términos de la funcionalidad de "fluido de reemplazo". Esta funcionalidad no se acepta como característica técnica ya que no define específicamente la estructura de la invención".

"Las reivindicaciones 3, 4, 6, 7, 10, 11, 13 y 14 no son claras porque usan términos imprecisos como "aproximadamente" y "cantidad suficiente para elevar el nivel". Estos términos no permiten distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un término preciso o un rango concreto".

"Las reivindicaciones 6, 7, 13 y 14 no son claras porque definen el objeto de la solicitud en términos del resultado a alcanzar de "elevar el nivel de citrulina en plasma del paciente", y no caracterizan la composición, puesto que las reivindicaciones de esta forma incluyen no sólo la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Se sugiere reemplazarlo por las características esenciales, estructurales o funcionales, que contribuyen a la obtención de ese efecto".

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“Las reivindicaciones 10, 11, 13 y 14 no son claras porque mencionan un método pero este no se caracteriza correctamente. Se recuerda que un método debe caracterizarse mediante una secuencia lógica de etapas y las condiciones técnicas específicas”.

R/: El solicitante se permite manifestar lo siguiente:

El Examinador señala que la **Reivindicación 1** no está clara, porque describe un término de la funcionalidad de "**fluido de reemplazo**", sin embargo, en la descripción de la invención se describe que el fluido de reemplazo de la hemoconcentración puede ser un fluido estándar (por ejemplo, Plasmalyte) usado en cirugía. Por ejemplo, Plasmalyte es una solución isotónica no pirogénica estéril. Estos fluidos son bien conocidos en la técnica, sin embargo, la adición de citrulina a ellos no era conocida en la técnica. (Ver **Anexo II**. Plasma-Lyte 148; **Anexo III** Plasma-Lyte A Official FDA information, side effects and uses; **Anexo IV** Continuous venovenous hemofiltration with citrate-based replacement fluid: efficacy, safety, and impact on nutrition).

Para mayor claridad, se ha **modificado la Reivindicación 1** donde se define la composición de la invención, la cual comprende citrulina y un fluido de reemplazo de hemoconcentración.

Con relación a las **Reivindicaciones 3, 4, 6, 10, 11 y 13 (Nuevas Reivindicaciones 2, 3, 5 y 6)** se eliminó el término “aproximadamente”.

Con respecto a la objeción de las **Reivindicaciones 6 y 13 (Nuevas Reivindicaciones 5 y 10)** se **modificó** la expresión "cantidad suficiente para elevar el nivel", por la expresión “**una cantidad por encima de**”

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La **Reivindicación 8 (Nueva Reivindicación 6)** del método para la fabricación de una composición, el solicitante la **modificó** con el fin de determinar las etapas que comprenden dicho método. Por lo cual se **eliminó la Reivindicación 8** anterior.

Por lo anteriormente mencionado, el solicitante pone a consideración del Examinador de Patentes un **NUEVO CAPITULO REIVINDICATORIO**, el cual incluye **diez (10) nuevas reivindicaciones** en dos folios.

Por lo anterior, estamos dando cumplimiento a lo exigido en el Examen de Forma notificado mediante Oficio No. 1402 del 13 de febrero de 2018 y solicitamos respetuosamente se **CONTINÚE** con el trámite de la presente solicitud de Patente de Invención titulada “**ADMINISTRACIÓN INTRAVENOSA DE CITRULINA DURANTE LA CIRUGÍA**” a nombre de la sociedad **VANDERBILT UNIVERSITY**, para las **nuevas Reivindicaciones 1 a 10 inclusive**.

Atentamente,



JAIME EDUARDO DELGADO VILLEGAS

C.C. No. 19.270.955 Bogotá

T.P. No. 43.308 C.S.J.

Anexos:

Nuevas Reivindicaciones (10) en dos folios.

Anexo I Documento Aucella et al. Lesión Renal Aguda, en 5 folios.

Anexo II Documento PLASMA-LYTE 148, en 8 folios.

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Anexo III Documento Plasma-Lyte A Official FDA information, side effects and uses, en 8 folios.

Anexo IV Continuous venovenous hemofiltration with citrate-based replacement fluid: efficacy, safety, and impact on nutrition, en dos folios.

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MDE



Mario Delgado Echeverri e Hijos Ltda.

Abogados Consultores – Marcas y Patentes

I (We) undersigned / Se dirige a usted Janis Elsner citizen, adult and living in (ciudadano, mayor y vecino de) Tennessee, USA in my position of legal Representative of the company (en mi condición de Representante legal de la firma) **VANDERBILT UNIVERSITY** with headquarters in (domiciliada en) 2201 West End Avenue 305 Kirkland Hall Nashville, Tennessee 37240 (US), Estados Unidos.

Grant ample an sufficient power of attorney to: **JAIME EDUARDO DELGADO VILLEGAS** and/or **CLEMENCIA DELGADO VILLEGAS**, attorneys, adults, residing in Bogotá (Colombia), so that on our behalf and representation, carry out in Colombia the patent application title **INTRAVENOUS ADMINISTRATION OF CITRULLINE DURING SURGEY** Application Number NC2018/0000768. The representatives are authorized with broad powers in order to receive, desist, grant and others when it was necessary according with our interests; in the event that such procedures shall be transferred unto a judicial field, the legal representatives are authorized to act as plaintiff or defendant before the competent authorities, having an ample power to settle, to submit to arbitration, to waive, to present appeals and all other necessary special faculties.

Confiero poder general, amplio y suficiente a los Dres. **JAIME EDUARDO DELGADO VILLEGAS**, y/o **CLEMENCIA DELGADO VILLEGAS**, Abogados, mayores y vecinos de Bogotá, D.C. (Colombia), para que en nuestro nombre y representación adelanten en Colombia la solicitud de patente **ADMINISTRACIÓN INTRAVENOSA DE CITRULINA DURANTE LA CIRUGÍA** Expediente NC2018/0000768. Los Apoderados quedan con amplias facultades para recibir, desistir, transigir, sustituir y lo demás que fuere necesario en pro de nuestros intereses; y en caso de que el procedimiento debiera pasar a conocimiento judicial, quedan facultados para actuar como demandantes o demandados ante los Jueces que sean competentes, con poder amplio, pudiendo transar, someter a árbitros, desistir, interponer recursos y con todas las demás facultades especiales que fueren necesarias.

For that purpose, I kindly request to grant ample powers to our attorneys, who shall be able to exercise the functions independently or collectively.

Con éste objeto, ruego le confieran personería suficiente a nuestros Apoderados quienes podrán obrar en forma conjunta o independiente e incluso sustituir el presente poder.

Granted and signed today / Dado y firmado hoy

Feb 15, 2018

In / en Nashville, TN, USA

By / por Janis Elsner

Signature / Firma

Director of Commercial Operations
Center for Technology Transfer
and Commercialization

REIVINDICACIONES MODIFICADAS

1. Una composición **CARACTERIZADA PORQUE** comprende citrulina y un fluido de reemplazo de hemoconcentración.
2. La composición de la Reivindicación 1, **CARACTERIZADA PORQUE** la citrulina está entre 100-300 $\mu\text{mol/L}$.
3. La composición de la Reivindicación 1, **CARACTERIZADA PORQUE** la citrulina está en 200 $\mu\text{mol/L}$.
4. La composición de cualquiera de las Reivindicaciones 1 a 3, **CARACTERIZADA PORQUE** la composición se formula y se administra durante cirugía de bypass cardiopulmonar
5. La composición de una cualquiera de las Reivindicaciones 1 a 4, **CARACTERIZADA PORQUE** la citrulina está presente en una cantidad suficiente para mantener el nivel de citrulina en plasma del paciente por encima de 100 $\mu\text{mol/L}$ después de la administración.
6. Un método para la fabricación de una composición medicinal **CARACTERIZADO PORQUE** comprende:
 - agregar citrulina en una cantidad por encima de 100 mmol/l al fluido de reemplazo de la hemoconcentración, con el cual se eleva el nivel de citrulina en plasma del paciente;
 - formular la composición medicinal de administración al paciente sometido a derivación cardiopulmonar durante la cirugía.

7. El método de la Reivindicación 6, **CARACTERIZADO PORQUE** donde la composición se administra durante cirugía, al paciente cuando se somete a bypass cardiopulmonar.
8. El método de la Reivindicación 6 o 7, **CARACTERIZADO PORQUE** la citrulina es de 100-300 $\mu\text{mol/L}$.
9. El método de cualquiera de las Reivindicaciones 6 a 8, **CARACTERIZADO PORQUE** la citrulina está a 200 $\mu\text{mol/L}$.
10. El método de cualquiera de las Reivindicaciones 6 a 9, **CARACTERIZADO PORQUE** la citrulina está presente en una cantidad suficiente para mantener el nivel de citrulina en plasma del paciente por encima de 100 $\mu\text{mol/L}$.

.....

Dialysate and Replacement Fluid Composition for CRRT

Filippo Aucella, Salvatore Di Paolo, Loreto Gesualdo

Department of Nephrology, Dialysis and Transplantation, University of Foggia,
Foggia, Italy

Abstract

Continuous renal replacement therapies (CRRTs) are increasingly used in order to maintain normal or near-normal acid-base balance in intensive care unit (ICU) patients. Acid-base balance is greatly influenced by the type of dialysis employed and by the administration route of replacement fluids. In continuous veno-venous hemofiltration, buffer balance depends on losses with ultrafiltrate and gain with replacement fluid, while in techniques such as continuous veno-venous hemodiafiltration, clinicians should balance the role of the dialysate. The type of buffer greatly influences not only acid-base correction, but also clinical outcome. Lactate or bicarbonate fluids are currently used, but recent studies suggest that bicarbonate-buffered replacement fluids can improve acid-base status and reduce cardiovascular events better than lactate fluids. The buffer concentration should exert a buffer load that may compensate for deficits, for losses in the buffer process, and for extracorporeal losses and should therefore usually be supraphysiological. However, the dialysate buffer or electrolyte concentration need always to be balanced with that of the replacement fluids employed. Both fluids should contain electrolytes in concentrations aiming for a physiologic level and taking into account preexisting deficits or excess and all input and losses. Clinicians should be aware that in CRRTs the quality control for sterility, physical properties, individualized prescription and balance control are vitally important.

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Major changes have occurred in the medical management of intensive care unit (ICU) patients over the past two decades, and the role of extracorporeal blood treatments has broadened from conventional renal function replacement to a series of non-renal conditions.

Continuous renal replacement therapies (CRRTs) have found widespread use and acceptance because they incorporate several advantages, such as improved hemodynamic stability, gradual urea removal without fluctuations,

and optimal fluid balance. Further, they obviate the need of nutritional restrictions in terms of both the volume and composition of the nutrients administered to critically ill patients [1].

In this setting, we need to keep in mind that patients with acute renal failure (ARF) depend on dialysis to maintain fluid and electrolyte balance. One crucial goal of CRRT in the treatment of ARF patients is to achieve and maintain normal or near-normal acid-base balance over time, thereby preventing the detrimental effects of acidemia on cardiovascular performance, hepatic metabolism and hormonal response [2]. Over the course of the procedure solutes are ultrafiltered or diffused between blood and dialysate such that the plasma composition is restored toward normal values. Obviously, the makeup of the dialysate and the replacement fluid, in combination with the features of the dialysis technique [3], are of paramount importance to accomplish this goal.

Choice of Buffer and Acid-Base Balance

Acid-base balance is greatly influenced by the type of dialysis technique employed, diffusion and convection being differently balanced. Moreover, the type of buffer in both replacement fluid and dialysate greatly influences not only acid-base correction, but also clinical outcome.

The dialysis techniques have a clear influence on buffer kinetics. Despite a comparable blood and dialysate/replacement fluid flow rate, different techniques are associated with varying effects on electrolyte and acid-base homeostasis.

In continuous veno-venous hemofiltration (CVVH) the buffer balance depends on buffer losses with the ultrafiltrate and buffer gain with the replacement fluid. If patients undergo isolated ultrafiltration, without infusing any replacement fluid, for example in chronic cardiac failure, bicarbonate losses are compensated by the reduction in the distribution volume of the buffer, such that bicarbonate serum levels do not change significantly [3]. When replacement fluids are infused along with fluid ultrafiltration, bicarbonate losses in the ultrafiltrate need to be balanced by equal amounts in the infusion solution. In the clinical setting, metabolic acidosis is the most frequent condition occurring in these patients and a positive buffer balance is commonly required. Moreover, clinicians need to be aware that the bicarbonate concentration in the ultrafiltrate is higher than the plasma level, because of a sieving coefficient of >1 .

In continuous veno-venous hemodialysis (CVVHD), a pure diffusive technique, buffer balance is a function of the concentration gradient between the dialysate and blood, and a feedback between the base balance and blood bicarbonate also occurs. Thus, the correction of acidosis depends only on the buffer concentration in the dialysate [1, 3].

In techniques with both diffusive and convective processes, such as continuous veno-venous hemodiafiltration (CVVHDF), the buffer gain depends on both the dialysate and the replacement fluid, with the inherent risk of alkalemia. A comparison of CVVHDF and CVVH showed that they had a significantly different impact on bicarbonate and sodium control [4]. Specifically, CVVH was associated with a lower incidence of metabolic acidosis and a higher incidence of metabolic alkalosis [4], possibly due to small differences in the total amount of buffer infused during CVVH.

Which Buffer Should Be Preferred in CRRT?

Lactate, acetate, and bicarbonate have all been used as buffers during CRRT. Citrate has been used as a buffer and anticoagulant. Although bicarbonate is the natural buffer, bicarbonate-based solutions have not been available until recently, because of the higher risk of bacterial contamination and the instability of this buffer in the presence of calcium and magnesium ions. Moreover, the rate of administration of buffer solutions during CRRT is definitely lower than during discontinuous treatments, because the accumulation of acetate or lactate has rarely been reported, although this may be an important point in high-volume treatments [5]. It is now clear that lactate or bicarbonate fluids offer a better control of acid-base balance and improved cardiovascular stability compared to acetate fluids [5]. In clinical practice, both lactate and bicarbonate ions are used in replacement fluids and in dialysate for CRRT. These buffers have shown similar efficacy in correcting metabolic acidosis [6]. Obviously, lactate infusion increases serum lactate levels and this might lead to a misleading interpretation of the clinical situation. Solutions containing lactate are contraindicated in patients with concomitant lactic acidosis and in those with lactate intolerance, defined as a rise of 5 mmol/l during CRRT: these patients are at a high risk of worsening acidosis because of insufficient conversion of lactate into bicarbonate in the face of ongoing bicarbonate losses. Currently, lactate concentrations vary from 45 mmol/l (chloride 103 mmol/l) down to 35 mmol/l (chloride 110 mmol/l), and these differences in solute composition can lead to clinical consequences, namely to the development of hypochloremic metabolic alkalosis after several days of CRRT with high lactate/low chloride solutions, or hyperchloremic metabolic acidosis when a low lactate/high chloride fluid is used [5]. Moreover, several studies suggest that lactate-buffered replacement fluids can exert negative effects on different metabolic and hemodynamic parameters [2]. In ICU patients suffering from multiple organ dysfunction, the conversion of lactate to bicarbonate is frequently impaired and the resulting increase in blood

lactate concentration may exert multiple negative effects. On the other hand, the administration of bicarbonate in patients with lactic acidosis has also been questioned, although CRRT makes it possible to overcome some of the unwanted effects of bicarbonate infusion, e.g. volume overload, hyperosmolarity, and a decrease in ionized calcium.

Bicarbonate-buffered replacement fluids are presently considered a valuable approach to improve the prognosis of critical ill patients with ARF. Several, but not all, studies support the view that bicarbonate-buffered replacement fluids can improve acid-base status and reduce the incidence of cardiovascular events in ICU patients, when compared with lactate-buffered fluids [7]. This suggestion should be viewed in light of the peculiar milieu of the critically ill patient, the specific features of which (systemic inflammation, increased energy expenditure and metabolic activation, cardiovascular stress, hyperdynamic cardiovascular response) cause a clinical picture characterized by an excess of lactate production, even in the absence of an increase in blood lactate levels, increased oxygen consumption and elevated protein catabolism. Blood lactate, if not further metabolized, acts as a strong anion, which has the same acidifying effect of chloride. Accordingly, iatrogenic hyperlactatemia can cause a state of metabolic acidosis. When oxidizable anions are used in replacement fluids, these anions, acetate, lactate or citrate, need to be completely oxidized to CO_2 and H_2O in order to generate bicarbonate and then the buffering capacity equals that of bicarbonate solutions. However, on the contrary, if metabolic conversion is not adequate, the increased blood concentration of the anions leads to an acidotic condition. The type and extent of these acid-base changes are governed by the intensity of plasma water exchange/dialysis, by the buffer content of the replacement fluids, and by the actual metabolic rate of the above-mentioned anions.

The advantage of using a buffer-free replacement solution is that the dose of bicarbonate can be titrated according to a given target value of base excess, which may vary according to the clinical picture of the ICU patient, as well as to specific treatment modalities, such as permissive hypercapnia. The application of a lung-protective strategy with reduced tidal volumes, effective lung recruitment, adequate positive end-expiratory pressure to minimize alveolar collapse during expiration, and permissive hypercapnia has been shown to be advantageous in adult patients who have acute respiratory distress syndrome [8]. Indeed, strategies such as permissive hypercapnia or permissive hypoxemia have been reported to favor the onset of ARF by compromising renal blood flow [9]. Therefore, the correction of acidosis, as suggested by the NIH protocol Acute Respiratory Distress Syndrome Network [10], has been questioned as experimental evidence and preliminary clinical data indicate that buffering hypercapnic acidosis abrogates its protective effects [11, 12]. Nevertheless,

patients with permissive hypercapnia may require huge amounts of buffer to correct acidosis, the infusion of the buffer itself leading to a further increase in CO_2 production, thus leading to a vicious circle which, in the presence of limited CO_2 elimination, may worsen the acidotic state of the patient. The infusion of lactate in this condition does not appear appropriate because relatively more lactate than bicarbonate is required to achieve the same base excess target. In conclusion, the most reliable method to control respiratory acidosis of permissive hypercapnia, is the administration of lactate-free fluids and bicarbonate titration according to the requirements of individual patients [13].

The paradigmatic CRRT technique using bicarbonate-buffered replacement solutions is acetate-free CVVH (AF-CVVH) [14]. The technique is based on separate infusion of water and electrolytes administered pre-filtration, and isotonic sodium bicarbonate administered post-filtration. The setting of the technique is based on a model predicting the bicarbonate infusion rate for a targeted plasma bicarbonate level. Indeed, AF-CVVH allows fast control of acidosis and has the main advantage of separately controlling urea retention and metabolic acidosis in patients with severe ARF and cardiovascular instability. This method offers the possibility of titrating the amount of the buffer given more precisely, and has been used to treat severe metabolic acidosis.

A further particular point is the use of citrate for regional anticoagulation in CRRT. One absolute requirement for CRRT is anticoagulation which can expose patients to the risk of bleeding. Citrate anticoagulation may limit such risk, but the prevention of citrate side effects requires meticulous monitoring. Then, since citrate is metabolized to bicarbonate, each citrate ion producing three bicarbonate ions, no additional anionic base is required to control metabolic acidosis [5]. When adopting citrate anticoagulation, normal saline is infused as a predilution fluid, while a special hyponatremic dialysate is required because of the sodium load due to trisodium citrate and saline infusion. The amount of citrate to infuse is titrated on the basis of coagulation parameters, or on surrogate parameters, such as the total calcium-ionized calcium rate, and not on a target base excess. Consequently, the use of citrate may be associated with both metabolic alkalosis and acidosis [1]. Metabolic alkalosis is more common in patients with hepatic dysfunction or in those requiring support with large amounts of blood products containing acid citrate dextrose as anticoagulant. In this setting, alkalosis may be prevented using a high chloride load, i.e. large volumes of normal saline as predilution fluid, and infusing calcium chloride. When required, bicarbonate losses may be enhanced by increasing the dialysate flow or the predilution saline infusion. Metabolic acidosis may also occur in the presence of hypercitratemia and hypercalcemia, usually in the setting of ARF with rhabdomyolysis.

Fluid Composition

Electrolyte balance during ARF treated with CRRT is largely dependent on the electrolyte plasma concentration available for ultrafiltration, the ultrafiltration rate and the composition of the replacement solution. As CRRT works continuously, serious derangement in fluid and electrolyte homeostasis may occur in the absence of careful prescription and extremely vigilant monitoring [15].

Replacement fluids for CVVH should contain the following concentrations of electrolytes and glucose: sodium 140 mmol/l; chloride 108–112 mmol/l; potassium 0–4 mmol/l; calcium 1.5–1.75 mmol/l; magnesium 0.5–0.75 mmol/l, and glucose 0–15.00 mg/l [1].

Sodium

Sodium balance can be rather different according to the different CRRT techniques. In CVVH, a totally convective therapy, the value of ultrafilterable sodium must be taken into account to choose the correct sodium concentration in the substitution fluid [15]. It is worth remembering that the sodium concentration in the ultrafiltrate is around 7 mEq/l lower than the plasma water sodium concentration, because a certain amount of the total ion is complexed with anions, particularly with bicarbonate and proteins. When using techniques which combine diffusive and convective processes, such as CVVHD or CVVHDF, a dialysis solution is added to the system. Even with these techniques sodium transport is mainly due to the convective process; the diffusive flux is definitely lower and is strongly influenced by the sodium concentration of the dialysate. A retrospective study showed that CVVHDF was more likely to achieve serum sodium concentrations within the normal range than CVVH, thereby supporting the role of dialysate in the maintenance of an adequate sodium concentration [4]. It has been suggested that a supraphysiological sodium concentration in the dialysate or replacement solutions would improve the hemodynamic stability or prevent the increase in intracranial pressure, but there are no conclusive data concerning this issue [6].

Potassium

Hyperkalemia is a typical feature of ARF, particularly in the presence of tissue breakdown (crush syndrome, hemolysis, hypercatabolic syndromes). Unless important hyperkalemia is present, 3–4 mEq/l potassium needs to be added to the replacement fluid in CVVH in order to avoid hypokalemia. In techniques comprising a diffusive process, namely CVVHD or CVVHDF, the content of potassium in the dialysate must be titrated to about 2–4 mEq/l, to avoid the risk of hypokalemia [15]. The very slow flux of potassium from cells to the

extracellular space would possibly contribute to the high hemodynamic tolerance of CRRT.

Divalent Ions

About 60% of total plasma calcium is ultrafilterable, then substitution fluid in CVVH must contain about 3 mEq/l of calcium in order to prevent hypocalcemia. When mixed techniques, such as CVVHD, are used, the dialysate concentration of calcium usually ranges from 3 to 3.5 mEq/l. Patients undergoing an exchange of very large volumes of ultrafiltrate during CRRT may be prone to the risk of a positive calcium balance, and therefore may require a lower content of calcium in replacement fluids. The same cautions are required to keep an appropriate magnesium balance.

Intensive schedules of CRRT can easily induce hypophosphatemia in the critically ill patient, the risk being magnified by prolonged parenteral nutrition, malnourishment or concomitant metabolic alkalosis. This condition may require oral or parenteral supplementation with phosphate salts, as well as supplementation of dialysate solutions. The addition of phosphate salts to the dialysate and/or the replacement solutions facilitates phosphate handling, while the risk of phosphate precipitation in the presence of calcium ions has recently been excluded [16].

Glucose

The recent publication of a randomized trial showing a significant survival advantage with strict glucose control in critically ill patients has important consequences for CRRT with glucose-containing dialysate or substitution fluids [17]. The use of physiologic concentrations of glucose in the dialysate and in replacement fluids is advised to prevent or compensate extracorporeal losses, while glucose-free solutions might be used when an adequate nutritional regimen has been established [6].

A special case is that of critically ill children weighing <10 kg who require blood as a priming solution for the extracorporeal circuit before initiating CRRT to prevent hemodilution and to maintain adequate oxygenation [18]. Blood preparations usually contain supraphysiological electrolyte concentrations and a nonphysiological acid-base balance that may exacerbate the critical condition of the small patient. In such cases, the pretreatment of blood bank-derived blood aimed to normalize pH and electrolyte concentration yields more physiological blood priming.

In conclusion, due to its continuous nature, CRRT need to be carefully monitored for the composition of dialysate and replacement fluids to avoid dangerous electrolyte imbalance. Moreover, it is possible that in the near future we

may see more sophisticated CRRT solutions containing nutrients and antioxidants that may improve the outcome of ICU patients.

Physical Properties

All lactate-based or buffer-free solutions are acidic, while bicarbonate-based fluids have a physiological pH. Experimental findings suggest that acidic fluids cause intracellular acidosis and reduced activity of macrophages and blood mononuclear cells [5].

The use of replacement fluids or dialysate solutions at room temperature as well as continuous blood flow through the extracorporeal system cause an average 2°C reduction in body temperature, and an energy loss of about 1,000 kcal/day [1]. Although the clinical significance of this effect is not clear at this point, the energy loss measured during CVVHD has been suggested to be important in hemodynamic stability or even for patient prognosis [19]. Heat loss and consequent hypothermia may also affect immune functions and increase the risk of clotting of the CRRT circuit. The extent of these effects depends on the length of the circuit, on the flow rate of blood, replacement fluids and dialysate, on body weight and finally on the presence or absence of an intact autoregulatory mechanism to preserve core temperature. A heating device may avoid the above-cited side effects; on the other hand a lower body temperature may be desirable in patients with excessive oxygen consumption and low systemic vascular resistance. At present, it is not clearly known in which patients the net effect of CRRT-induced hypothermia is useful or harmful.

Obviously substitution fluids need to be sterile, and the same is true for the dialysate, not only in high-flux dialysis schedules when backfiltration is most likely to occur, but also in other continuous dialytic treatments. As in intermittent treatments, the feasibility of online production of substitution fluids in CRRT has recently been evaluated.

Administration Route

The CRRT prescription directly affects electrolyte and acid-base balance [5, 6, 20]. In diffusive or mixed dialysis schedules, the concentration of electrolytes in the blood is dependent on the corresponding concentration in the dialysate and in replacement fluids. In pure convective treatments most ions pass freely across the membrane, showing a sieving coefficient of around one. In this case the ionic concentration of the substitution fluids should be very similar to that of normal plasma, with an alkaline pH.

The different features of predilution (lower solute clearance, higher ultrafiltration rate and larger filter surface area) and of postdilution (higher filtration fraction) are well known [1, 5, 6, 20]. Predilution may be preferred to reduce the need for heavy anticoagulation or to enhance the ultrafiltration rate, especially relevant for HV-CVVH. Possibly, pre- and postdilution may be combined when extracorporeal clearance is limited by an inadequate blood flow, but this point deserves future studies.

Conclusions

The great complexity of current CRRT schedules, exchanging up to 50 l/day, has been made possible by the development of specialized dialysate and replacement fluid solutions. These strategies have been supported by studies reporting an improvement in the survival of the critically ill patient following the adoption of technical approaches providing the exchange of large amounts of fluids, and/or the use of high dialysate flows. However, with the increase in exchanged volumes, the control of fluid sterility, physical properties and composition, and the choice of individualized prescriptions are becoming increasingly crucial in the single ICU patient.

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PLASMA-LYTE 148 (An Electrolyte Solution) Injection/ PLASMA-LYTE A (An Electrolyte Solution) Injection

Baxter

Description

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection are sterile, nonpyrogenic intravenous solutions which contain no bacteriostatic or antimicrobial agents or added buffers. The composition, osmolarity and approx. pH of the individual solutions are shown in Table 1.

Normal physiologic isotonicity range is approximately 280 – 310 mOsmol/litre. PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection have an osmolarity of 294 mOsmol/litre.

Table 1	DIN	Size (mL)	Composition (g/L)					Osmolarity (mOsmol/L)	pH	Ionic Concentration (mmol/L)								Caloric Content (kcal/L)	
			Sodium Chloride, USP	Potassium Chloride, USP	Sodium Gluconate, USP	Sodium Acetate, USP	Magnesium Chloride, USP			Sodium	Potassium	Chloride	Magnesium	Calcium	Acetate	Gluconate	Lactate		Dextrose
PLASMA-LYTE 148 Injection (JB2534)	00260576	1000	5.26	0.37	5.02	3.68	0.30	294	6.0 (4.0 – 8.0)	140	5	98	1.5	0	27	23	0	0	15
PLASMA-LYTE A Injection (JB2544)	02339358	1000	5.26	0.37	5.02	3.68	0.30	294	7.4 (4.0 – 8.0)	140	5	98	1.5	0	27	23	0	0	15

Actions

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection are a source of water for hydration and provide electrolytes. Both are capable of inducing diuresis depending on the clinical conditions of the patient. See Table 1 for ionic concentrations of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection.

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection both contain acetate and gluconate anions which produce a metabolic alkalinizing effect. These anions are metabolized in the liver to glycogen, and ultimately to carbon dioxide and water, which requires the consumption of hydrogen cations.

Indications

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection are indicated for volume replacement, as a source of water and electrolytes, and as an alkalinizing agent.

Contraindications

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection are contraindicated in patients with a known hypersensitivity to the product. [See WARNINGS AND PRECAUTIONS]

Warnings and Precautions

General

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection are not indicated for the treatment of hypochloremic hypokalemic alkalosis and should be used with caution, if at all, in patients with hypochloremic hypokalemic alkalosis (e.g., due to prolonged vomiting, pyloric stenosis, prolonged nasogastric suctioning).

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection are not indicated for the primary treatment of severe metabolic acidosis.

Although PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection have a potassium concentration similar to the concentration in plasma, it is insufficient to produce a useful effect in case of severe potassium deficiency; therefore, it should not be used for correction of severe potassium deficiency.

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection are not indicated for the treatment of hypomagnesemia.

Warnings

Hypersensitivity Reactions

Hypersensitivity/infusion reactions, including anaphylactoid reactions, have been reported with PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection.

The infusion must be stopped immediately if any signs or symptoms of a suspected hypersensitivity reaction develop. Appropriate therapeutic countermeasures must be instituted as clinically indicated.

Risk of Fluid and/or Solute Overload and Electrolyte Disturbances

Depending on the volume and rate of infusion, the intravenous administration of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection can cause

- fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration/hypervolemia, congested states, pulmonary edema or acid-base imbalance.

The risk of dilutional states is inversely proportional to the electrolyte concentrations of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection.

Clinical evaluation and periodic laboratory determinations may be necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient or the rate of administration warrants such evaluation.

Use in Patients with or at Risk for Hypermagnesemia

Solutions containing magnesium should be used with caution, if at all, in patients with

- hypermagnesemia or conditions predisposing to hypermagnesemia, including but not limited to severe renal impairment or magnesium therapy such as for eclampsia.
- myasthenia gravis.

Use in Patients with or at Risk for Alkalosis

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection should be administered with particular caution, if at all, to patients with alkalosis or at risk for alkalosis.

Excess administration of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection can result in metabolic alkalosis.

Use in Patients with Hypervolemia or Overhydration, or Conditions that Cause Sodium Retention and Edema

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection should be administered with particular caution, if at all, to hypervolemic or overhydrated patients.

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection should be administered with particular caution, if at all, to patients with conditions that may cause sodium retention, fluid overload and edema, such as patients with primary hyperaldosteronism, secondary hyperaldosteronism (associated with, for example, hypertension, congestive heart failure, renal artery stenosis, or nephrosclerosis), or preeclampsia.

Use in patients with Hypocalcemia

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection contains no calcium, and an increase in plasma pH due to its alkalinizing effect may lower the concentration of ionized (not protein-bound) calcium. PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection should be administered with particular caution, if at all, to patients with hypocalcemia.

Use in Patients with or at Risk for Hyperkalemia

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection should be administered with particular caution, if at all, to patients with hyperkalemia or conditions predisposing to hyperkalemia (such as severe renal impairment or adrenocortical insufficiency, acute dehydration, or extensive tissue injury or burns) and in patients with cardiac disease.

Use in Patients with Severe Renal Impairment

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection should be administered with particular caution, if at all, to patients with severe renal impairment. In such patients administration of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection may result in sodium and/or potassium or magnesium retention.

Risk of Air Embolism

Do not connect flexible plastic containers in series in order to avoid air embolism due to possible residual air contained in the primary container.

Pressurizing intravenous solutions contained in flexible plastic containers to increase flow rates can result in air embolism if the residual air in the container is not fully evacuated prior to administration.

Use of a vented intravenous administration set with the vent in the open position could result in air embolism.

Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.

Precautions

Caution must be exercised in the administration of parenteral fluids, especially those containing sodium ion, to patients receiving corticosteroids or corticotropin.

Special Populations

Use in Pediatric Patients

Safety and effectiveness of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection in children have not been established by adequate and well controlled trials.

Use in Geriatric Patients

When selecting the type of infusion solution and the volume/rate of infusion for a geriatric patient, consider that geriatric patients are generally more likely to have cardiac, renal, hepatic, and other diseases or concomitant drug therapy.

Pregnancy and Lactation

There are no adequate data from the use of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection in pregnant or lactating women. The potential risks and benefits for each specific patient should be carefully considered before using PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection in pregnant or lactating women.

Monitoring and Laboratory Tests

There have been reports of false-positive test results using the Bio-Rad Laboratories Platelia Aspergillus EIA test in association with the use of Baxter gluconate-containing PLASMA-LYTE solutions. Therefore, positive test results for this test in patients receiving Baxter gluconate-containing PLASMA-LYTE solutions should be interpreted cautiously and confirmed by other diagnostic methods.

Adverse Reactions

This list of adverse reactions in this Direction Sheet is based on postmarketing reports (see below).

If any adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures, and save the remainder of the fluid and administration set for examination if deemed necessary.

Post-marketing Adverse Reactions

The following adverse reactions have been reported in the postmarketing experience, with unspecified PLASMA-LYTE products and PLASMA-LYTE products without Dextrose, listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.

IMMUNE SYSTEM DISORDERS: Hypersensitivity/infusion reactions, including Anaphylactoid reaction, and the following manifestations: Tachycardia, Palpitations, Chest pain, Chest discomfort, Dyspnea, Respiratory rate increased, Flushing, Hyperemia, Asthenia, Feeling abnormal, Piloerection, Edema peripheral, Pyrexia

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Infusion site reactions (e.g., Infusion site pain, Burning sensation)

Class Reactions

Other adverse reactions reported with PLASMA-LYTE products with Dextrose are:

- Other manifestations of hypersensitivity/infusion reactions:
Hypotension, Wheezing, Urticaria, Cold sweat, Chills
- **Hyperkalemia**

Drug Interactions

Caution is advised when administering PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection to patients treated with drugs that may increase the risk of sodium and fluid retention, such as corticosteroids or corticotropin [See also WARNINGS AND PRECAUTIONS].

Caution is advised when administering PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection to patients treated with drugs for which renal elimination is pH dependent. Due to its alkalinizing effect (formation of bicarbonate), PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection may interfere with the elimination of such drugs.

- Renal clearance of acidic drugs such as salicylates, barbiturates, and lithium may be increased.
- Renal clearance of alkaline drugs such as sympathomimetics (e.g., ephedrine, pseudoephedrine), quinidine, or dextroamphetamine (dexamphetamine) sulfate, may be decreased.

Because of its potassium content, PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection should be administered with caution in patients treated with agents or products that can cause hyperkalemia or increase the risk of hyperkalemia, such as potassium sparing diuretics (amiloride, spironolactone, triamterene), with ACE inhibitors, angiotensin II receptor antagonists, or the immunosuppressants tacrolimus and cyclosporine.

Dosage and Administration

Dosing Considerations

As directed by a physician. Dosage, rate, and duration of administration are to be individualized and depend upon the indication for use, the patient's age, weight, clinical condition, and concomitant treatment, and on the patient's clinical and laboratory response to treatment.

PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection are intended for intravenous administration using sterile equipment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer unless the solution is clear and the seal is intact.

When introducing additives to PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection, aseptic technique must be used. Mix the solution thoroughly when additives have been introduced. Do not store solutions containing additives [See ADDITIONS]

Administration

Directions for use of VIAFLEX Plastic Container

The VIAFLEX plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146 Plastic). 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 can leach out certain of its chemical components in very small amounts within the expiration period, e.g. di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

Do not remove unit from overwrap until ready for use.

To Open:

Tear overwrap down side at slit and remove solution container. Visually inspect the container. If the outlet port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired. If supplemental medication is desired, follow directions below before preparing administration. Some opacity of the plastic due to moisture absorption during sterilization process may be observed. This is normal and does not affect the solution quality and safety. The opacity will diminish gradually. Check for leaks by squeezing inner bag firmly. If leaks are found discard solution as sterility may be impaired.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

To Add Medication:

1. Prepare medication site.
2. Using a syringe and a 20 – 22 gauge needle, puncture resealable rubber plug at target area and inject. Multiple additions may be made in this manner.
3. Mix solution and medication thoroughly. For high density medications such as potassium chloride, squeeze ports while ports are upright and mix thoroughly.

Risk of Air Embolism

Do not connect flexible plastic containers in series in order to avoid air embolism. [See WARNINGS AND PRECAUTIONS]

Additions

Additives may be incompatible with PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection. Complete information is not available.

As with all parenteral solutions, compatibility of the additives with the solution must be assessed before addition. Before adding a substance or medication, verify that it is soluble and/or stable in water and that the pH range of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection is appropriate. After addition, check for a possible color change and/or the appearance of precipitates, insoluble complexes or crystals.

The instructions for use of the medication to be added and other relevant literature must be consulted.

Additives known or determined to be incompatible must not be used.

If in the informed judgment of the physician it is deemed advisable to introduce additives, aseptic technique must be used. Mix the solution thoroughly when additives have been introduced. Do not store solutions containing additives.

Overdosage

Excessive administration of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection may lead to metabolic alkalosis. Metabolic alkalosis may be accompanied by hypokalemia as well as a decrease in ionized serum calcium and magnesium.

An excessive volume of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection may lead to fluid and sodium overload with a risk of edema (peripheral and/or pulmonary), particularly when renal sodium excretion is impaired.

Excessive administration of potassium may lead to the development of hyperkalemia, especially in patients with severe renal impairment.

Excessive administration of magnesium may lead to hypermagnesemia.

When assessing an overdose, any additives in the solution must also be considered.

The effects of an overdose may require immediate medical attention and treatment.

Storage

Store at 15°C to 25°C.

Special Handling Instructions

After opening the container, the contents should be used immediately and should not be stored for a subsequent infusion.

Do not reconnect any partially used containers.

Dosage Form, Composition and Packaging

How Supplied

Table 1 shows the composition, osmolarity, approx pH, calories/litre and ionic concentration of PLASMA-LYTE 148 Injection/PLASMA-LYTE A Injection.

<https://www.drugs.com/pro/plasma-lyte-a.html>

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Home › Drugs by Condition › F › Fluid Retention › Lvp solution Prescribing Information

Plasma-Lyte A

Generic Name: sodium chloride, sodium gluconate, sodium acetate, potassium chloride and magnesium chloride

Dosage Form: injection, solution

Plasma-Lyte A Injection

pH 7.4 (Multiple Electrolytes Injection, Type 1, USP)

in VIAFLEX Plastic Container

Plasma-Lyte A Description

Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) is a sterile, nonpyrogenic isotonic solution in a single dose container for intravenous administration. Each 100 mL contains 526 mg of Sodium Chloride, USP (NaCl); 502 mg of Sodium Gluconate (C₆H₁₁NaO₇); 368 mg of Sodium Acetate Trihydrate, USP (C₂H₃NaO₂•3H₂O); 37 mg of Potassium Chloride, USP (KCl); and 30 mg of Magnesium Chloride, USP (MgCl₂•6H₂O). It contains no antimicrobial agents. The pH is adjusted with sodium hydroxide. The pH is 7.4 (6.5 to 8.0).

Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) administered intravenously has value as a source of water, electrolytes, and calories. One liter has an ionic concentration of 140 mEq sodium, 5 mEq potassium, 3 mEq magnesium, 98 mEq chloride, 27 mEq acetate, and 23 mEq gluconate. The osmolarity is 294 mOsmol/L (calc). Normal physiologic osmolarity range is 280 to 310 mOsmol/L. Administration of substantially hypertonic solutions may cause vein damage. The caloric content is 21 kcal/L.

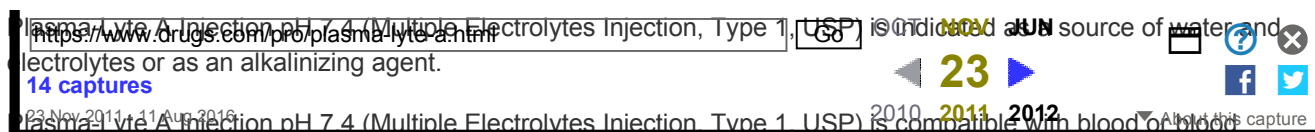
The VIAFLEX plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146 Plastic). The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

Plasma-Lyte A - Clinical Pharmacology

Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) has value as a source of water and electrolytes. It is capable of inducing diuresis depending on the clinical condition of the patient.

Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) produces a metabolic alkalizing effect. Acetate and gluconate ions are metabolized ultimately to carbon dioxide and water, which requires the consumption of hydrogen cations.

Indications and Usage for Plasma-Lyte A



Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) is compatible with blood or blood components. It may be administered prior to or following the infusion of blood through the same administration set (i.e., as a priming solution), added to or infused concurrently with blood components, or used as a diluent in the transfusion of packed erythrocytes. Plasma-Lyte A Injection and 0.9% Sodium Chloride Injection, USP are equally compatible with blood or blood components.

Contraindications

None known

Warnings

Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) should be used with great care, if at all, in patients with congestive heart failure, severe renal insufficiency, and in clinical states in which there exists edema with sodium retention.

Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) should be used with great care, if at all, in patients with hyperkalemia, severe renal failure, and in conditions in which potassium retention is present.

Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) should be used with great care in patients with metabolic or respiratory alkalosis. The administration of acetate or gluconate ions should be done with great care in those conditions in which there is an increased level or an impaired utilization of these ions, such as severe hepatic insufficiency.

The intravenous administration of Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states, or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the injection. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of the injection.

In patients with diminished renal function, administration of Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) may result in sodium or potassium retention.

Precautions

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.

Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) should be used with caution. Excess administration may result in metabolic alkalosis.

Caution must be exercised in the administration of Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) to patients receiving corticosteroids or corticotropin.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Animal reproduction studies have not been conducted with Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP). It is also not known whether Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and effectiveness of Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) in pediatric patients have not been established by adequate and well controlled trials, however, the use of electrolyte solutions in the pediatric population is referenced in the medical literature. The warnings, precautions and adverse reactions identified in the label copy should be observed in the pediatric population.

Geriatric Use

Clinical studies of Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

Do not administer unless solution is clear and seal is intact.

Drug/Laboratory Test Interactions

There have been reports of positive test results using the Bio-Rad Laboratories Platelia Aspergillus EIA test in patients receiving Baxter gluconate containing Plasmalyte solutions. These patients were subsequently found to be free of Aspergillus infection. Therefore, positive test results for this test in patients receiving Baxter gluconate containing Plasmalyte solutions should be interpreted cautiously and confirmed by other diagnostic methods.

Adverse Reactions

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, and save the remainder of the fluid for examination if deemed necessary.

Plasma-Lyte A Dosage and Administration

As directed by a physician. Dosage is dependent upon the age, weight and clinical condition of the patient as well as laboratory determinations.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

All injections in VIAFLEX plastic containers are intended for intravenous administration using sterile equipment.

Additives may be incompatible. Complete information is not available. Those additives known to be incompatible should not be used. Consult with pharmacist, if available. If, in the informed judgment of the physician, it is deemed advisable to introduce additives, use aseptic technique. Mix thoroughly when additives have been introduced. Do not store solutions containing additives.

How is Plasma-Lyte A Supplied

https://www.drugs.com/pro/plasma-lyte-a.html

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About this capture

Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) in VIAFLEX plastic containers is available as shown below:

Code	Size (mL)	NDC
2B2544	1000	NDC 0338-0221-04
2B2543	500	NDC 0338-0221-03

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. It is recommended the product be stored at room temperature (25°C); brief exposure up to 40°C does not adversely affect the product.

DIRECTIONS FOR USE OF VIAFLEX PLASTIC CONTAINER

Warning: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

To Open

Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired. If supplemental medication is desired, follow directions below.

Preparation for Administration

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

To Add Medication

Warning: Additives may be incompatible.

To add medication before solution administration

1. Prepare medication site.
2. Using syringe with 19 to 22 gauge needle, puncture resealable medication port and inject.
3. Mix solution and medication thoroughly. For high density medication such as potassium chloride, squeeze ports while ports are upright and mix thoroughly.

To add medication during solution administration

1. Close clamp on the set.
2. Prepare medication site.
3. Using syringe with 19 to 22 gauge needle, puncture resealable medication port and inject.
4. Remove container from IV pole and/or turn to an upright position.
5. Evacuate both ports by squeezing them while container is in the upright position.
6. Mix solution and medication thoroughly.

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 Baxter Healthcare Corporation
 23 Nov 2011 - 11 Aug 2016 2010 2011 2012
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Deerfield, IL 60015 USA

Printed in USA

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07-19-55-071

Rev. December 2007

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PACKAGE LABEL PRINCIPAL DISPLAY PANEL



PLASMA-LYTE® A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1, USP) Carton Label

2B2544X 14-1000 ML

VIAFLEX® CONTAINER

PLASMA-LYTE® A INJ PH 7.4 (MULTIPLE

ELECTROLYTES INJ, TYPE 1, USP)

EXP

XXXXX

SECONDARY BAR CODE

(17) YYMM00 (10) XXXXX

LOT

XXXXX

PRIMARY BAR CODE

(01) 50303380221047

NOTE: YY=Year, MM=Month and date will always be 00. Lot and Exp. Date added at time of printing.

Secondary bar code human readable is variable and will be

added at time of printing. The parenthesis are not

encoded in actual bar code.



Plasma-Lyte A Injection pH 7.4 (Multiple Electrolytes Injection Type 1 USP) 1000mL Container Label

<https://www.drugs.com/pro/plasma-lyte-a.html>

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ID: C09884221-04
 23 Nov 2011 - 11 Aug 2016

About this capture

Plasma-Lyte A

Injection pH 7.4

(Multiple Electrolytes Injection

Type 1 USP)

1000 mL

Each 100 mL contains 526 mg Sodium Chloride USP 502

mg Sodium Gluconate USP 368 mg Sodium Acetate

Trihydrate USP 37 mg Potassium Chloride USP 30 mg

Magnesium Chloride USP pH adjusted with Sodium

Hydroxide pH 7.4 (6.5 to 8.0) mEq/L Sodium 140

Potassium 5 Magnesium 3 Chloride 98 Acetate 27

Gluconate 23 Osmolarity 294 mOsmol/L (calc) Sterile

Nonpyrogenic Single dose container Additives may be

incompatible Consult with pharmacist if available When

introducing additives use aseptic technique Mix thoroughly

Do not store Dosage Intravenously as directed by a

physician See directions Cautions Squeeze and inspect

inner bag which maintains product sterility Discard if leaks

are found Must not be used in series connections Do not

use unless solution is clear Rx Only Store unit in

moisture barrier overwrap at room temperature

(25°C/77°F) until ready to use Avoid excessive heat See

insert

VIAFLEX container PL 146 plastic

BAXTER PLASMA-LYTE VIAFLEX and PL 146 are

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For product information 1-800-933-0303

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axter Healthcare Corporation

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44 capsules

00015 USA

23 Nov 2011 - 11 Aug 2016

Made in USA

Plasma-Lyte A

sodium chloride, sodium gluconate, sodium acetate, potassium chloride and magnesium chloride injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	NDC Product Code (Source)	0338-0221
Route of Administration	INTRAVENOUS	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SODIUM CHLORIDE (SODIUM CATION)	SODIUM CHLORIDE	526 mg in 100 mL
SODIUM GLUCONATE (SODIUM CATION)	SODIUM GLUCONATE	502 mg in 100 mL
SODIUM ACETATE (SODIUM CATION)	SODIUM ACETATE	368 mg in 100 mL
POTASSIUM CHLORIDE (POTASSIUM CATION)	POTASSIUM CHLORIDE	37 mg in 100 mL
MAGNESIUM CHLORIDE (MAGNESIUM CATION)	MAGNESIUM CHLORIDE	30 mg in 100 mL

Inactive Ingredients

Ingredient Name	Strength
WATER	
SODIUM HYDROXIDE	

Product Characteristics

Color		Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	NDC	Package Description	Multilevel Packaging
1	0338-0221-03	500 mL In 1 BAG	None
2	0338-0221-04	1000 mL In 1 BAG	None

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA017378	02/02/1979	

Labeler

<https://www.drugs.com/pro/plasma-lyte-a.html> (00003209)

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Name	Address	ID/FEI	Operations
BAXTER HEALTHCARE CORPORATION		059140764	MANUFACTURE

Revised: 12/2009

Baxter Healthcare Coporation

Continuous venovenous hemofiltration with citrate-based replacement fluid: efficacy, safety, and impact on nutrition.

Bihorac A¹, Ross EA.

Author information

Abstract

BACKGROUND: Citrate-based continuous venovenous hemofiltration (CVVH) replacement fluids provide effective and simple regional anticoagulation. However, concern over toxicity has limited citrate use, especially at the high filtration rates advocated for better outcomes. We used volumes of 72 L/d in patients at high risk for bleeding and investigated the treatment's efficacy, safety, and clinical results, especially with regard to nutrition supplementation.

METHODS: A standard replacement solution (trisodium citrate, 13.3 mmol/L) was infused at up to 3 L/h in predilution CVVH, and ultrafiltration was increased further for net fluid removal. Calcium was repleted centrally. We retrospectively evaluated metabolic control, citrate toxicity, circuit patency, hemorrhagic complications, hemodynamics, vasopressor use, nutrition, renal recovery, and mortality.

RESULTS: Seventy-six patients with 766 CVVH patient-days were analyzed. Mean replacement fluid rate was 31 mL/kg/h (35 mmol/h of citrate), with hemofiltration of 35 mL/kg/h (67 +/- 11 L/d). No significant bleeding, citrate toxicity, or hypocalcemia was observed, and 74% required additional alkali therapy. Dialyzer patency was 58% at 48 hours. Control of fluid, electrolytes, and azotemia was excellent (serum creatinine level, 1.7 mg/dL [150 micromol/L]; blood urea nitrogen, 42 mg/dL [15 mmol/L]). Fluid removal permitted protein (1.7 g/kg/d) and calorie (30 kcal/kg/d) nutrition in high fluid volumes. Vasopressor use and central pressures decreased significantly. Cumulative 28-day intensive care unit survival was 58%, and 41% of these patients had renal recovery in the intensive care unit. Thirty percent of the entire cohort survived the hospitalization, and 53% of these patients recovered renal function.

CONCLUSION: CVVH with 3 L/h of citrate-based replacement fluid is a safe, efficient, and simple technique in patients at high risk for bleeding. It allows superb control of uremia and fluid balance and thereby permits aggressive nutritional support.

Comment in

Citrate-based replacement solutions with continuous venovenous hemofiltration: not as simple as it sounds. [*Am J Kidney Dis.* 2006]

Publication type, MeSH terms, Substances ☐

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