Citric acid and citrates

GENERAL INFORMATION

Citric acid is used in effervescing mixtures and granules. Formulations that contain citric acid are used in the management of dry mouth and to dissolve renal calculi, alkalinize the urine, and prevent encrustation of urinary catheters. Citric acid is also an ingredient of citrated anticoagulant solutions.

Uses

Urinary calculi

Treatment of complex and large urinary calculi secondary to infection can be difficult, and complete removal of the stone may not always be possible. Residual stone fragment rates are 37% (range 10–57%) after percutaneous nephrolithotomy and 20% after anatrophic nephrolithotomy [1]. Technical advances in the management of urinary calculi have resulted in improved stone clearance rates in these cases. Owing to a combination of factors, such as large stone mass, associated infection, abnormal renal anatomy, and poor general health of the patient, infection stones can still pose a difficult treatment problem. This has resulted in the use of alternative (and minimally invasive) treatment options. Dissolution treatment, either alone or as adjuvant therapy, has been used. Citric acid, in various concentrations, has been used in dissolution treatment [2]. Citric acid, being a urinary acidifier, inhibits the formation of precipitates of calcium phosphate, calcium carbonate, and magnesium ammonium phosphate, and allows dissolution of stones. It may also help to reduce the size of calculi, allowing spontaneous elimination.

Citric acid has been used to treat 22 patients (10 men and 12 women, mean age 45, range 15–60 years; 23 affected kidneys) with kidney stones (14 staghorn calculi, four partial staghorn calculi, and five large-burden calculi) [3]. They underwent irrigation with solution R (citric acid monohydrate 6 g, magnesium carbonate 2.8 g, glucolactone 0.6 g, and water 100 ml) following debulking of the stone with percutaneous nephrolithotomy (n = 20), ureteroscopy, and shock wave lithotripsy (n = 2) combined with open procedures (n = 4). Irrigation was performed through a nephrostomy tube (n = 20) or in a retrograde fashion (n = 3) using a closed infusion pump system (40 ml/hour). The response to treatment was checked using a nephrostogram and/or plain X-ray. In six kidneys irrigation had to be abandoned because of loin pain, leak, or sepsis after an average duration of 2 (1–5) days. The average duration of irrigation was 6 (1–20) days. At the end of irrigation, four kidneys had complete radiographic clearance, and the stone was reduced to calyceal dust in three. There was a partial response in 11 and no response in five. Following alternative interventions in six cases (four with a partial response and two with no response), further clearance was achieved in three and calyceal dust in three. The response was better if the stone was reduced to less than 10 mm before irrigation. At the mean follow-up of 2.4 (1–4) years, of 13 kidneys with stone clearance or calyceal dust, nine suffered recurrence or re-growth, five of which required further interventions. Only four of the 23 kidneys remained stone-free.

In patients with complex stone disease, adjuvant solution R irrigation can reduce the stone burden, although the overall success rate is limited. However, there is a considerable potential for adverse effects, necessitating close monitoring for sepsis and electrolyte abnormalities.

Anticoagulation

In 2000 the FDA issued an urgent warning to all hospital pharmacies and hemodialysis units that triCitrasol, an unapproved formulation of sodium citrate that has been used as an anticoagulant to keep intravascular lines open, can cause death after intravenous infusion; triCitrasol is marketed in individual sterile 30 ml glass vials, distributed both individually and in hemodialysis kits [4]. A patient died of cardiac arrest shortly after the injection of triCitrasol 46.7% into a permanent hemodialysis blood access catheter that had just been implanted. Rapid or excessive infusion of citrate solutions can cause fatal cardiac dysrhythmias, seizures, or bleeding due to sequestration of blood calcium.

Cytosol Laboratories manufactured triCitrasol, and Medcomp distributed it. Both Cytosol Labs and Medcomp voluntarily recalled triCitrasol for use with blood access catheters. On 9 April 2000, Medcomp announced in a letter to its customers that it was recalling its kits (or trays) containing triCitrasol and the Medcomp Ash Split Catheter II for hemodialysis or apheresis, a blood separation and re-transfusion process. About 3000 Medcomp catheter kits with triCitrasol were distributed nationwide. They were also distributed in Puerto Rico and Canada.

The FDA urged hospital pharmacies and hemodialysis units across the USA to stop using the product. Alternative 4% solutions of citrate are available for use in these and most other medical settings.

ORGANS AND SYSTEMS

Cardiovascular

Citric acid toxicity has been reported previously, but only after intravenous administration. It was originally seen with massive transfusion of blood products with citrate as the anticoagulant. Two case reports have described accidental intravenous administration of citrate or citric acid; at a maximum serum concentration of citrate (4.1 mmol/l) there were profound alterations in blood pressure and QT interval; these were reversed by calcium infusion [5].

Metabolism

Although there is a long list of causes of metabolic acidosis with an increased anion gap [6,7], clinical clues can help diagnosis. A case report has illustrated the acute metabolic and hemodynamic effects of ingestion of a massive load of oral citric acid. The principal findings included a

metabolic acidosis accompanied by an increase in the plasma anion gap, not due to lactic acidosis, hyperkalemia, and the abrupt onset of hypotension [8].

- A 42-year-old previously healthy male prisoner drank a large volume of a commercial solution of unknown composition. His medical history was non-contributory, except for severe epigastric pain. Within an hour, his condition deteriorated; he was ashen, his blood pressure was 80/40 mmHg, and his pulse rate was 102/minute. His neck vessels were flat and his breath sounds were equal bilaterally, with occasional expiratory wheezes at both bases. There were no cardiac murmurs. The abdomen was soft and the bowel sounds were active. His extremities were warm with no cyanosis or edema. There were no neurological abnormalities. Fortuitously, because of therapy to avoid cardiac complications of hyperkalemia, he was given 1 g of calcium chloride, 50 mmol of sodium bicarbonate, 25 g of glucose, and 10 units of regular insulin intravenously. His blood pressure immediately increased to 116/76 mmHg and his pulse rate fell to 90/minute. By the next morning his plasma acid-base balance was normal, as was his ionized calcium concentration (1.1 mmol/l).

Because of the short duration and severity of the metabolic acidosis, together with a near-normal lactate concentration, acid ingestion was the most likely cause for his acid-base disorder. This diagnosis was confirmed once the composition of the ingested fluid was known.

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