Research Report

Hydrochloric Acid Infusion for the Treatment of Metabolic Alkalosis in Surgical Intensive Care Unit Patients

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Abstract

Background: Older reports of use of hydrochloric acid (HCl) infusions for treatment of metabolic alkalosis document variable dosing strategies and risk. **Objectives:** This study sought to characterize use of HCl infusions in surgical intensive care unit patients for the treatment of metabolic alkalosis. **Methods:** This retrospective review included patients who received a HCl infusion for >8 hours. The primary end point was to evaluate the utility of common acid-base equations for predicting HCl dose requirements. Secondary end points evaluated adverse effects, efficacy, duration of therapy, and total HCl dose needed to correct metabolic alkalosis. Data on demographics, potential causes of metabolic alkalosis, fluid volume, and duration of diuretics as well as laboratory data were collected. **Results:** A total of 30 patients were included, and the average HCl infusion rate was 10.5 ± 3.7 mEq/h for an average of 29 ± 14.6 hours. Metabolic alkalosis was primarily diuretic-induced (n = 26). Efficacy was characterized by reduction in the median total serum CO_2 from 34 to 27 mM/L ($P < 0.001$). The change in chloride ion deficit and change in apparent strong ion difference (SIDa) were not correlated with total HCl administered. There were no documented serious adverse effects related to HCl infusions. **Conclusion:** HCl was effective for treating metabolic alkalosis, and no serious adverse events were seen. In this clinical setting, the baseline chloride ion deficit and SIDa were not useful for prediction of total HCl dose requirement, and serial monitoring of response is recommended.

Keywords

acid-base balance, clinical practice, critical care, nephrology, surgery

Introduction

The use of hydrochloric acid (HCl) for the treatment of metabolic alkalosis has been reported in the literature since the 1960s. The reported dosing strategies and risk of adverse effects varied. HCl infusions are typically used in severe or refractory metabolic alkalosis and are rarely recommended as an initial treatment option. At the University of Rochester Medical Center, the use of HCl is primarily in the management of mild to moderate metabolic alkalosis secondary to use of continuous infusion of chloruretic, loop diuretics. At our institution, intravenous HCl is the treatment of choice for surgical intensive care unit (SICU) patients with diuretic-induced chloride depletion alkalosis who have poor or limited response to acetazolamide, who have concomitant renal failure, or in whom there is associated markedly elevated total serum CO_2 (tCO_2; eg, >38 mM/L).

HCl is not commercially available and must be extemporaneously compounded from concentrated, sterilized HCl solution. At our institution, the HCl is added to sterile water for injection in glass containers using Millex-FG 0.2micron hydrophobic filters (Merck Millipore Ltd, Cork, Ireland), which are specifically designed for acids and are chemically safe, utilizing a Biohazard Safety Cabinet (Vertical Flow BSC) with appropriate Personal Protective Equipment. Dose

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requirements are typically based on the patient's base excess or chloride ion deficit. Typical concentrations are 0.1 or 0.2 N (100-200 mmol Cl^-/L). Concentrations greater than 0.2 N have been associated with hemolysis and are, therefore, not recommended.[1-4] Infusions of HCl have been well tolerated when administered through the distal port of a central intravenous catheter,[1-20] with only rare reports of significant tissue necrosis, emphasizing the need to confirm the proper placement of central catheters prior to infusion.[21-23] At our institution, HCl infusions are typically stopped based on clinical judgment and close monitoring of individual response (eg, when the underlying cause of the metabolic alkalosis is removed or resolved and the acid-base disturbance is corrected). Ongoing monitoring includes complete blood count (CBC) and electrolytes, blood gases, and vigilant observation of the infusion site and surrounding tissues.

The purpose of this retrospective study was to summarize and evaluate our experience with the use of intravenous HCl in SICU patients, with a focus on evaluating the utility of common acid-base equations for predicting total HCl dose requirements. We also evaluated the effectiveness, safety, and indication for HCl therapy. This study was approved by and conducted in compliance with requirements of the University of Rochester Institutional Review Board, and informed consent was waived.

Materials and Methods

A retrospective review of the medical record was completed for all patients who received greater than 8 hours of HCl infusion while admitted to the SICU service from January 1, 2004, to December 31, 2005. Patients were identified by querying the pharmacy records for the manufacturing and dispensing of HCl during the timeframe stated above.

Demographic information was collected, including age (if greater than 90 years, we recorded >90), gender, height, weight, and race or ethnic group data. Primary reason for ICU admission and potential causes of and contributors to metabolic alkalosis were recorded. The total input and output of fluids during the ICU admission, as recorded on daily flow sheets, were calculated up to the point of the initiation of diuresis. The duration and dose of loop diuretics administered were collected along with total input and output of fluids during the exposure to diuretics. The volume of gastric secretions lost via nasogastric (NG) tube was recorded. Total blood products received from the time of admission until 24 hours after the conclusion of the HCl infusion were recorded. All available laboratory values were recorded starting at the initiation of diuresis and continuing through 24 hours after the conclusion of the HCl infusion. These values include chemistries (sodium, chloride, creatinine, phosphate, corrected ionized calcium, albumin, potassium, total carbon dioxide, blood urea nitrogen, magnesium, lactate, and lactate dehydrogenase) and arterial blood gases (pH, pCO_2, pO_2, and bicarbonate). Data on hematological parameters were also collected (hemoglobin, hematocrit, abnormal RBC morphology). The infusion rate, total dose, and incremental doses of HCl were recorded. The incremental doses of HCl corresponded with the times of the serial laboratory values available for the patient. For each set of laboratory data that provided adequate data, chloride ion deficit and apparent strong ion difference (SIDa) were calculated. The following equations were used to calculate SIDa and chloride ion deficit:

$$\text{SIDa} = \left(Na^+ + K^+ + Ca^{2+} + Mg^{2+}\right) - \left(Cl^- + \text{lactate}^-\right).$$

When a measured lactate concentration was not available, a normal value of 1 mEq/L was used to permit estimation of the SIDa. When a measured ionized calcium was not available, a normal value of 4.5 mEq/L was used to permit estimation of the SIDa. The potential errors from these estimations have a very small impact on SIDa results.

$$\begin{aligned}\text{Chloride ion deficit} &= \left(0.2\ \text{L/kg} \times \text{Body weight}\ [\text{kg}]\right) \\ &\times \left(\left[Cl^-\right]\text{Normal} - \left[Cl^-\right]\text{Corrected}\right) \\ \left[Cl^-\right]\text{Corrected} &= \left[Cl^-\right]\text{Observed} \\ &\times \left(\left[Na^+\right]\ \text{Normal} / \left[Na^+\right]\ \text{Observed}\right),\end{aligned}$$

where $[Cl^-]$ Normal = 103 mM/L and $[Na^+]$ Normal = 140 mM/L.

Any adverse effects from the HCl infusion, as documented in the medical record, were recorded. In addition, any biochemical evidence of adverse events, including moderate to severe metabolic acidosis (tCO_2 <15 mM/L or arterial pH <7.25), or laboratory findings consistent with red blood cell hemolysis were recorded.

All data are reported using appropriate descriptive statistics based on the distribution and normality of the data. Comparison of results before and after HCl infusion was done using the Wilcoxon signed rank test. The relationship between SIDa or chloride ion deficit and total HCl dose were evaluated using simple linear regression analysis. All analyses were considered descriptive and exploratory, and no sample size or power analysis was conducted.

Results

The results of the pharmacy database query found records for 32 patients who had orders for HCl infusions. One patient never received the HCl infusion (unknown reason), and 1 patient failed to meet the inclusion criteria of >8 hours of total infusion time. Therefore, 30 patients were included in this study. Demographic information for the 30 patients is presented in Table 1.

Table 1. Demographic Data and Results.

Number of patients	30
Age, years (median, range)	65 (23-84)
Male (%)	19 (63.3%)
Race (%)	
Caucasian	27 (90)
African American	2 (6.7)
Native American	1 (3.3)
Causes of metabolic alkalosis (%)	
Loop diuretics	26 (86.7)
Blood product transfusions	3 (10)
Unknown	1 (3.3)
pH, median (range)[a]	7.5 (7.36-7.59)
CO_2 (mmol/L), median (range)[a]	34 (28-42)
pCO_2 (mm Hg), median (range)[a]	45 (30-65)
SIDa, mean (SD)[a]	46.6 (3.5)
SCr (mg/dL), mean (SD)[a]	1.3 (0.7)
HCl infused (mEq), mean (SD)	289 (168)
Duration of HCl infusion (hours), mean (SD)	29 (14.6)
Average infusion rate (mEq/h), mean (SD)	10.5 (3.7)
pH, median (range)[b,c]	7.42 (7.26-7.47)
CO_2 (mmol/L), median (range)[b]	(20-32)

Abbreviations: SCr, serum creatinine; SIDa, apparent strong ion difference.
[a]At initiation of hydrochloric acid (HCl) infusion.
[b]Near termination of HCl infusion.
[c]pH (Blood gas) only available for 14 individuals.

The mean total milliequivalents (mEq) of HCl received, the total duration of the infusion, and average HCl infusion rate (mEq/h) are provided in Table 1. The average HCl infusion rate was 10.5 ± 3.7 mEq/h (4-16.6 mEq/h). The average duration of the HCl infusion was 29.0 ± 14.6 hours (9 to 68 hours).

The potential causes of metabolic alkalosis were evaluated for each patient who received a HCl infusion. A total of 26 patients were infused with HCl following sustained loop diuretic therapy, 3 patients following large blood product administration (>20 units of blood products received prior to HCl infusion), and 1 patient with an unknown mechanism for metabolic alkalosis (no loop diuretic administered, no significant NG losses, and no blood products received). Patients were primarily general surgery, vascular surgery, and liver transplant patients.

Figure 1 illustrates the change in tCO_2 from pre–HCl infusion to post–HCl infusion, which was characterized by a reduction in the median tCO_2 from 34 to 27 mM/L ($P < 0.001$).

The total HCl administered was not correlated with the change in chloride ion deficit ($r = 0.058$; $P = 0.764$). There was also no significant association between total HCl administered and change in SIDa ($r = 0.145$; $P = 0.453$).

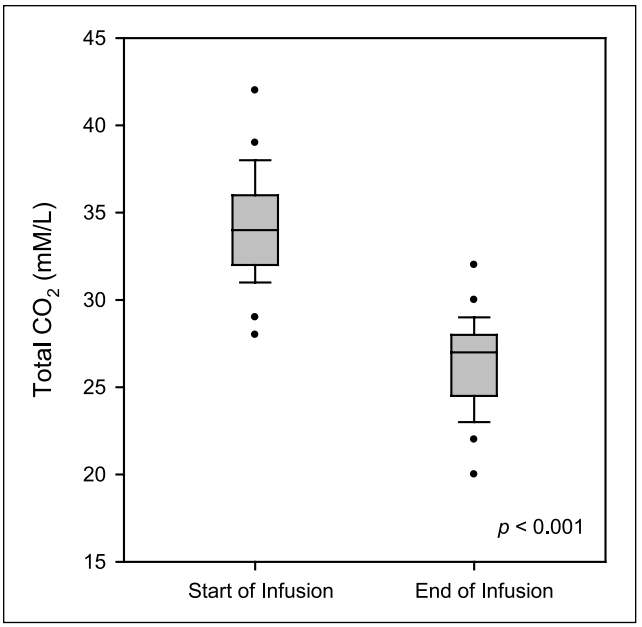

Figure 1. Box plot of total serum CO_2 (tCO_2) at the start and end of the hydrochloric acid (HCl) infusion. The horizontal line in the box represents the median; the interquartile range is represented by the box; and the whiskers are the 10th and 90th percentiles.

There were no serious adverse effects documented in the medical record related to the HCl infusions, no documented cases of tissue necrosis or extravasation injuries, and no cases of moderate to severe metabolic acidosis (pH < 7.25 or tCO_2 < 15 mM/L) during or following the HCl infusion. Evaluation of CBC results, including microscopy during the HCl infusions, revealed no evidence of hemolysis.

Discussion

Metabolic alkalosis is a common, if not relatively overlooked, finding in critically ill patients and may present with concomitant metabolic acidosis. This acid-base disorder is classically described as being either "chloride responsive" or "chloride resistant," with hypochloremic, hyperbicarbonatemic alkalosis ("chloride responsive") being the predominant form seen in the ICU. This form of metabolic alkalosis is also referred to as chloride-depletion metabolic alkalosis (CDA). The most common underlying causes of CDA in the critically ill are loss of HCl from gastric secretions (vomiting or large-volume NG aspiration of gastric contents) and the administration of chloruretic diuretics. Other contributing factors may include delayed or incomplete recovery from hypercapnic acidosis, large-volume blood transfusion, administration of alkali, and liver failure.[24-26]

The critically ill surgical patient often requires aggressive volume resuscitation in the early hours to days of their

care in the ICU to maintain organ perfusion and decrease the risk of multiple organ failure. Once the patient is hemodynamically stable, off all vasopressor support, and no longer requiring volume resuscitation, relatively aggressive diuretic therapy is often initiated. The goals of this therapy include promoting the loss of excess extracellular fluid and shortening the time to extubation and transfer out of the ICU, thereby avoiding adverse sequelae associated with prolonged mechanical ventilation and extended ICU stays. At our site, diuresis is most commonly achieved by administering a continuous infusion loop diuretic to maximize diuretic efficacy and efficiency and achieve the greatest overall net fluid loss. One of the most common complications that limits the extent of diuresis is the development of a "contraction alkalosis" with elevation of tCO_2 to >30 mM/L, without other clinical evidence of intravascular volume depletion. Effective treatment of this CDA will often allow continued diuresis. Administration of sodium chloride in the form of crystalloid IV solutions would be an effective treatment for CDA but is counterproductive to removing the excess extracellular fluid and facilitating weaning from mechanical ventilation. Many ICU patients will not tolerate large doses of potassium chloride to reverse the chloride deficit. Ammonium chloride or arginine monochloride have been recommended in the past, but they are often a poor choice in patients with underlying liver or renal disease and are no longer commercially available.

Alternative treatment options for ICU patients with diuretic-induced CDA include acetazolamide and HCl.[24-30] Acetazolamide has been shown to be effective in reducing hyperbicarbonatemia in critically ill patients with mild to moderate metabolic alkalosis[27-30] and is often used as a first-line agent for the treatment of diuretic-induced CDA. Typical practice at our institution is to administer at least 2 doses of acetazolamide (eg, 500 mg daily ×2 days) before consideration is given to starting an HCl infusion. In our experience, with continued administration of the loop diuretic infusion, acetazolamide has a moderate and short-lived effect on reducing tCO_2. It is relatively slow to work, with nadir tCO_2 observed at 16 to 24 hours after the dose,[29,30] and is relatively ineffective in the setting of significant renal insufficiency.

Advantages of HCl therapy include a direct correction of the underlying chloride deficiency, absence of need for end-organ metabolism or elimination, titration of the infusion rate to a desired tCO_2, the ability to stop the treatment when goals are achieved, and the low cost of the infusion. Disadvantages include the lack of a commercially available preparation, necessitating expertise and capabilities in manufacturing of sterile IV solutions, and the risk of serious extravasation injury.

Intravenous HCl is considered a treatment option for SICU patients at our institution with diuretic-induced CDA who have a poor or limited response to acetazolamide, concomitant renal failure, or a markedly elevated tCO_2 (eg, >38 mM/L). The use of HCl infusions has been reported in the literature for more than 40 years; however, most reports discuss its use in severe or refractory metabolic alkalosis,[1-20,22] with only a few authors advocating it as a rational earlier treatment option.[3,6,18] There are no reports in the literature describing the use of HCl infusion consistent with our application to reverse diuretic-induced CDA with the clinical intent of permitting continued diuresis of a patient without clinical evidence of intravascular volume depletion. This study was not of adequate design, nor did it intend to evaluate the efficacy of HCl to permit continued diuresis or shorten the duration of mechanical ventilation, but was limited to evaluating the biochemical response to treatment.

Limitations of this study are consistent with it being a single-center, retrospective chart review, including the potential for missing or inadequately documented information in the medical record. A total of 30 patients were reviewed, which therefore limited our ability to evaluate the relationship between laboratory parameters and total dose of HCl. In addition, many of the patients continued to receive chloruretic diuretics during the HCl infusion period, which would limit the predictive value of baseline laboratory data for estimating the total HCl infusion dose needed to correct hyperbicarbonatemia. Not all patients had ideal laboratory parameters to calculate a pre–HCl infusion versus post–HCl infusion SIDa or chloride ion deficit because we had to use the data closest to the start and stop of the HCl infusion based on routine clinical monitoring as opposed to accurately timed samples relative to the infusion. In future prospective studies, a complete laboratory workup, including necessary values for SIDa and chloride ion deficit, immediately prior to initiation of HCl therapy, at frequent times during the infusion, and 12 to 24 hours following completion of the infusion, is recommended. The lack of association between the chloride ion deficit and HCl dose is also likely related to other fluid losses and other potential sources of chloride.

There are reported cases in the literature of chest wall necrosis,[21,23] with 1 fatal outcome[21] following HCl infusion therapy. There was no documented clinical or laboratory evidence of safety issues with HCl therapy in our patient sample; however, given the small sample size, any conclusions about the overall safety of this therapy cannot be stated with confidence. To reduce the risk of extravasation and tissue injury, it is recommended that HCl only be infused using a central venous catheter, that the location of the catheter be confirmed radiographically prior to the start of the infusion, and that the HCl solution be infused using the most distal port of the catheter.

Conclusions

In this case series, HCl infusions were associated with a significant reduction in tCO_2 for SICU patients with predominantly diuretic-induced metabolic alkalosis, and no

serious adverse events were observed. The total HCl received (in mEq) was not correlated with changes in SIDa or chloride ion deficit, suggesting their limited predictive value. Therefore, routine and frequent monitoring of response and adjustment of the infusion rate are recommended for the safe use of HCl infusions. It is also strongly recommended that a firm policy be in place for the use of HCl, including that it is only infused through the distal port of a properly placed central venous catheter.

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Declaration of Conflicting Interests

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References

1. Beach FX, Jones ES. Metabolic alkalosis treated with intravenous hydrochloric acid. *Postgrad Med J*. 1971;47:516-520.
2. Bradham GB. The intravenous use of hydrochloric acid in the treatment of severe alkalosis. *Am Surg*. 1968;34:551-554.
3. Brimioulle S, Berre J, Dufaye P, Vincent JL, Degaute JP, Kahn RJ. Hydrochloric acid infusion for treatment of metabolic alkalosis associated with respiratory acidosis. *Crit Care Med*. 1989;17:232-236.
4. Brimioulle S, Vincent JL, Dufaye P, Berre J, Degaute JP, Kahn RJ. Hydrochloric acid infusion for treatment of metabolic alkalosis: effects on acid-base balance and oxygenation. *Crit Care Med*. 1985;13:738-742.
5. Bustamante EA, Levy H. Severe alkalemia, hyponatremia, and diabetic ketoacidosis in an alcoholic man. *Chest*. 1996;110:273-275.
6. Finkle D, Dean RE. Buffered hydrochloric acid: a modern method of treating metabolic alkalosis. *Am Surg*. 1981;47:103-106.
7. Harken AH, Gabel RA, Fencl V, Moore FD. Hydrochloric acid in the correction of metabolic alkalosis. *Arch Surg*. 1975;110:819-821.
8. Knutsen OH. New method for administration of hydrochloric acid in metabolic alkalosis. *Lancet*. 1983;1:953-956.
9. Kwun KB, Boucherit T, Wong J, Richards Y, Bryan-Brown CW. Treatment of metabolic alkalosis with intravenous infusion of concentrated hydrochloric acid. *Am J Surg*. 1983;146:328-330.
10. McDonald BR, Steiner RW. Rapid infusion of HCl during citrate dialysis to counteract alkalosis. *Clin Nephrol*. 1990;33:255-256.
11. Reisman RI, Puri VK. Prolonged intravenous hydrochloric acid infusion for severe metabolic alkalosis. *Intensive Care Med*. 1982;8:301-303.
12. Rothe KF. Hydrochloric acid for metabolic alkalosis. *Lancet*. 1983;1:1332.
13. Rowlands BJ, Tindall SF, Elliott DJ. The use of dilute hydrochloric acid and cimetidine to reverse severe metabolic alkalosis. *Postgrad Med J*. 1978;54:118-123.
14. Shavelle HS, Parke R. Postoperative metabolic alkalosis and acute renal failure: rationale for the use of hydrochloric acid. *Surgery*. 1975;78:439-445.
15. Wagner CW, Nesbit RR Jr, Mansberger AR Jr. Treatment of metabolic alkalosis with intravenous hydrochloric acid. *South Med J*. 1979;72:1241-1245.
16. Wagner CW, Nesbit RR Jr, Mansberger AR Jr. The use of intravenous hydrochloric acid in the treatment of thirty-four patients with metabolic alkalosis. *Am Surg*. 1980;46:140-146.
17. Williams DB, Lyons JH Jr. Treatment of severe metabolic alkalosis with intravenous infusion of hydrochloric acid. *Surg Gynecol Obstet*. 1980;150:315-321.
18. Williams SE. Hydrogen ion infusion for treating severe metabolic alkalosis. *Br Med J*. 1976;1:1189.
19. Worthley LI. The rational use of i.v. hydrochloric acid in the treatment of metabolic alkalosis. *Br J Anaesth*. 1977;49:811-817.
20. Worthley LI. Intravenous hydrochloric acid in patients with metabolic alkalosis and hypercapnia. *Arch Surg*. 1986;121:1195-1198.
21. Buchanan IB, Campbell BT, Peck MD, Cairns BA. Chest wall necrosis and death secondary to hydrochloric acid infusion for metabolic alkalosis. *South Med J*. 2005;98:822-824. doi:10.1097/01.smj.0000172781.27664.87
22. Frick PG, Senning A. Treatment of severe metabolic alkalosis with parenteral administration of 1/10 to 1/5 N hydrochloric acid [in German]. *Helv Med Acta*. 1963;30:603-607.
23. Jankauskas SJ, Gursel E, Antonenko DR. Chest wall necrosis secondary to hydrochloric acid use in the treatment of metabolic alkalosis. *Crit Care Med*. 1989;17:963-964.
24. Adrogue HJ, Madias NE. Management of life-threatening acid-base disorders: second of two parts. *N Engl J Med*. 1998;338:107-111; comment. doi:10.1056/NEJM199801083380207
25. Khanna A, Kurtzman NA. Metabolic alkalosis. *Respir Care*. 2001;46:354-365.
26. Webster NR, Kulkarni V. Metabolic alkalosis in the critically ill. *Crit Rev Clin Lab Sci*. 1999;36:497-510. doi:10.1080/10408369991239286
27. Berthelsen P. Cardiovascular performance and oxyhemoglobin dissociation after acetazolamide in metabolic alkalosis. *Intensive Care Med*. 1982;8:269-274.
28. Dickinson GE, Myers ML, Goldbach M, Sibbald W. Acetazolamide in the treatment of ventilatory failure complicating acute metabolic alkalosis. *Anesth Analg*. 1981;60:608-610.
29. Marik PE, Kussman BD, Lipman J, Jraus P. Acetazolamide in the treatment of metabolic alkalosis in critically ill patients. *Heart Lung*. 1991;20:455-459.
30. Mazur JE, Devlin JW, Peters MJ, Jankowski MA, Iannuzzi MC, Zarowitz BJ. Single versus multiple doses of acetazolamide for metabolic alkalosis in critically ill medical patients: a randomized, double-blind trial. *Crit Care Med*. 1999;27:1257-1261.