JPPT | Clinical Investigation

Use of Arginine Hydrochloride in the Treatment of Metabolic Alkalosis or Hypochloremia in Pediatric Patients

Caroline M. Sierra, PharmD; Elvin A. Hernandez, DrPH, MPH, MCHES; and Kristine A. Parbuoni, PharmD

OBJECTIVES Dosing of arginine for treatment of hypochloremia or metabolic alkalosis is laborious and has inherent variability in dose selection. The primary objective of this study was to determine the efficacy of arginine in the treatment of metabolic alkalosis and hypochloremia. Secondary objectives were to determine an optimal dose, route, and frequency for arginine administration in the treatment of these conditions.

METHODS This single center, retrospective, descriptive study was conducted in children who received arginine for treatment of hypochloremia or metabolic alkalosis. Treatment success was assessed by measuring serum chloride and bicarbonate concentrations after arginine administration.

RESULTS Of the 464 orders analyzed, 177 met inclusion criteria in 82 unique patients. Fifty percent (n = 81) of arginine administrations used to manage hypochloremia saw normalization of abnormal chloride levels, and 83% (n = 62) of arginine administrations used to treat metabolic alkalosis saw normalization of abnormal bicarbonate levels. Patients who received arginine to resolve hypochloremia were statistically significantly more likely to have their hypochloremia resolve if they used alternative dosing methods compared to established dosing methods (76 vs. 5, p = 0.001). However, this relationship was not seen for patients with metabolic alkalosis (11 vs. 51, p = 1.000). The median percentage of calculated daily dose of arginine needed for resolution of hypochloremia was 59% and was 35% for metabolic alkalosis.

CONCLUSIONS Arginine is effective to improve metabolic alkalosis and hypochloremia. Established dosing methods are not more effective than other methods in resolving metabolic alkalosis or hypochloremia. Further prospective studies are warranted to validate these results.

KEYWORDS arginine; clinical pharmacy; critical care; dosing; electrolytes; hypochloremia; metabolic alkalosis; pediatrics

J Pediatr Pharmacol Ther 2018;23(2):111–118

DOI: 10.5863/1551-6776-23.2.111

Introduction

Metabolic alkalosis is common in mechanically ventilated critically ill infants and children. This may be due to retaining bicarbonate or adverse effects related to diuretic exposure. Diuretic use alters electrolyte balances, potentially leading to hypochloremia and alkalosis.[1] Metabolic alkalosis can have further untoward effects, including neuromuscular and cardiovascular complications and compensatory hypoventilation due to hypercarbia. As a result, metabolic alkalosis may increase the duration, or time to wean off, of mechanical ventilation.[2,3] Metabolic alkalosis can occur in nonventilated patients as well. Patients often require treatment to resolve these electrolyte abnormalities.

Acetazolamide has been established as a treatment option for metabolic alkalosis in pediatric patients who are critically ill[4] and in mechanically ventilated pediatric patients.[2] It has also been shown that acetazolamide can resolve metabolic alkalosis, while increasing serum chloride levels, in neonates and infants with chronic respiratory insufficiency.[1] The evidence is controversial regarding acetazolamide's utility in pediatric cardiac patients.[2,5] Other options for correcting hypochloremia include sodium chloride, potassium chloride,[6] and ammonium chloride,[7] but these are not without ramifications for other electrolytes.

Arginine hydrochloride (arginine) is labeled by the Food and Drug Administration to stimulate the pituitary gland to release human growth hormone. It has been proposed as a means of resolving both metabolic alkalosis and hypochloremia in pediatric patients.[8] Case studies have shown that hydrochloric acid can be efficacious in resolving alkalosis.[9,10] Arginine dosing is based on hydrochloric acid dosing as both contain equimolar amounts of chloride. Providing chloride should help correct metabolic alkalosis if the kidney is functioning normally.[6] There is also evidence that replacing chloride can not only correct alkalosis,[11–13] but also can resolve hypochloremia.

Determining the required dose of arginine requires several calculations that depend upon laboratory values and patient weight.[14] It also requires additional adjustments beyond the initial calculation.[14] For correction of chloride deficit, Martin and Matzke[14] proposed that the dose of hydrochloric acid be calculated as follows: Dose (mEq) = [0.2 liters/kg × body weight (kg) × (103 – observed sodium chloride)]. If correcting metabolic alkalosis, the dose of hydrochloric acid should be calculated using the following equation: Dose (mEq) = [0.5 liters/kg × body weight (kg) × (observed sodium bicarbonate – 24)]. When correcting metabolic alkalosis, Martin and Matzke[14] suggest administering one half of the calculated dose. They also suggest administering arginine intravenously over 12 hours, with laboratory assessment performed at least every 4 hours during the infusion. Conversely, arginine dosing as provided in tertiary resources suggests that one-half to two-thirds of the calculated dose be administered intravenously in both metabolic alkalosis and hypochloremia. These recommendations do not address the rate of administration.[15]

Because the dosing method proposed by Martin and Matzke[14] is laborious and due to the lack of evidence regarding its accuracy as a dosing calculation strategy, some have chosen to use more simplified dosing strategies, such as weight based dosing. Due to the variability in arginine dosing at our institution and to clarify the necessity of using this more laborious dosing strategy, this study was undertaken to validate the use of arginine in metabolic alkalosis and hypochloremia and to determine if the dosing strategy proposed by Martin and Matzke[14] is preferable to other strategies. The primary objective of this study is to determine the efficacy of arginine in the treatment of metabolic alkalosis and hypochloremia. The secondary objective is to determine an optimal dose, route, and frequency for arginine administration in the treatment of these conditions.

Materials and Methods

Study Design. We conducted an institutional review board approved, single-center, retrospective, cohort observational study in pediatric patients. We performed a medical chart review on patients between 0 and 18 years of age who received arginine between October 1, 2013, and October 1, 2015, at Loma Linda University Children's Hospital. Patients from both intensive care and non-intensive care units were included, as were ventilated and non-ventilated patients. Patients were excluded if they received arginine for a pituitary function test or urea cycle disorder, if they had no abnormalities in their chloride or bicarbonate laboratory values prior to arginine administration, or if they had insufficient laboratory data to analyze the effect of arginine administration. Some patients met multiple criteria for exclusion.

Patient demographic data including age, weight, and sex were collected. It was recorded if arginine was given to treat hypochloremia, metabolic alkalosis, or both. If patients received arginine for both conditions, these administrations were treated as unique events to resolve both metabolic alkalosis and hypochloremia. Information about arginine dose, route, and frequency of administration were also collected. These parameters were determined by the patients' providers. The dose prescribed was assessed to determine if it fit the parameters of the Martin and Matzke[14] dosing method (referred to here as the established dosing method) or if it followed another regimen (e.g., weight based, fixed dosing). Each administration of arginine was treated as a unique event if there was a change in arginine dose or frequency or if the administrations of arginine were separated by more than 72 hours. Documentation of hypersensitivity reaction to arginine and discontinuation of arginine due to side effects was also collected.

Table 1. Patient and Dosing Demographics and Results

Characteristics	Result
Male sex, %	55
Age on admission, yr	2.5 ± 4.62
Weight on admission, kg	11.28 ± 15.04
Daily arginine dose, mEq	19.9 ± 34.18
Baseline chloride level, mmol/L*	93.66 ± 3.82
Chloride levels normalized, n (%)	81 (50)
Baseline bicarbonate level, mmol/L†	32.45 ± 4.56
Bicarbonate levels normalized, n (%)	62 (83)

All data is displayed as mean ± standard deviation unless otherwise indicated.
* Normal range of serum chloride concentration = 98–109 mmol/L.
† Normal range of serum bicarbonate concentration = 23–33 mmol/L.

Serum chloride and bicarbonate values were recorded to determine the efficacy of arginine administration. Laboratory values prior to and after arginine use were included in the analysis if they were obtained within 72 hours of a dose of arginine. This time frame was determined based on the half-life of arginine and the time anticipated to see clinical effect. Normalization was defined as a return of either chloride and/or bicarbonate to within the normal range and was determined using the earliest value collected after arginine administration. Time to resolution of serum chloride and/or bicarbonate levels was calculated for each arginine administration. Patients who had abnormal baseline chloride and bicarbonate levels were compared separately in order to identify potential factors that might influence normalization of laboratory values (e.g., mean dose administered, baseline chloride, and/or bicarbonate levels). These data were also pooled for some analyses.

Statistical Analysis. Univariable and bivariable

Table 2. Arginine Dosing by Indication

Characteristic	Result
Hypochloremia	
Male sex, n (%)	49 (48)
Age on admission, yr	3 ± 5.03 (range 0.02–18)
Weight on admission, kg	12.14 ± 17.08 (range 1.17–99)
Daily arginine dose, mEq	17.27 ± 19.23
Oral administrations of arginine, n (%)	55 (54)
Administrations resulting in normalization, n (%)	24 (24)
Administrations using established method, n (%)	14 (14)
Hypercarbia	
Male sex, n (%)	7 (47)
Age on admission, yr	1.92 ± 4.2 (range 0.02–15.83)
Weight on admission, kg	9.97 ± 13.6 (range 2.26–53)
Daily arginine dose, mEq	16.8 ± 35.14
Oral administrations of arginine, n (%)	6 (40)
Administrations resulting in normalization, n (%)	11 (73)
Administrations using established method, n (%)	0 (0)
Hypochloremia and hypercarbia	
Male sex, n (%)	39 (65)
Age on admission, yr	1.86 ± 3.31 (range 0.01–13.57)
Weight on admission, kg	9.14 ± 10.44 (range 1.55–70)
Daily arginine dose, mEq	24.13 ± 50.98
Oral administrations of arginine, n (%)	22 (37)
Administrations resulting in normalization of chloride, n (%)	26 (43)
Administrations resulting in normalization of bicarbonate, n (%)	48 (80)
Administrations resulting in normalization of chloride and bicarbonate, n (%)	23 (38)
Administrations using established method for chloride, n (%)	11 (18)
Administrations using established method for bicarbonate, n (%)	6 (10)

All data is displayed as mean ± standard deviation unless otherwise indicated.

analyses were used to describe the ability of arginine to successfully treat metabolic alkalosis or hypochloremia. Univariable analysis was used to describe demographic and descriptive data. Bivariable analysis was used for categorical variables. Chi-square and Fisher's exact tests were used to analyze binary and categorical data and independent samples *t*-tests were used for continuous data.

Multivariable analysis attempted to identify any statistically significant associations between the independent variables and dependent variables. Dependent variables included route of administration, frequency of administration, and use of the established dosing method compared with other dosing methods. Independent variables were the time to resolution of chloride or bicarbonate levels.

Unless specified, data are presented as a mean ± SD. A p value ≤ 0.05 was considered statistically significant.

Results

Patients. Of the 464 orders for arginine analyzed, 177 met inclusion criteria in 82 unique patients. Orders were excluded for the following reasons: 142 involved use for pituitary testing, 209 had insufficient laboratory data, and 32 were excluded because baseline laboratory values were normal. Included patients were 55% male with a mean age of 2.5 ± 4.62 years (range 0–18 years) and mean weight of 11.28 ± 15.04 kg (range 1.17–99 kg) on admission. Demographic data are presented in Table 1.

Of the 177 included arginine orders, 102 were administered due to hypochloremia, 15 due to hypercarbia, and 60 due to both hypochloremia and hypercarbia. Baseline serum chloride and bicarbonate levels were 93.66 ± 3.82 mmol/L (range) and 32.45 ± 4.56 mmol/L

Table 3. Comparison of Variables in Pediatric Patients with Resolved and Unresolved Hypochloremia Following Arginine Administration

Variables	Hypochloremia		p value
	Resolved	Unresolved	
Mean age on admission, yr	1.723	4.22	0.02†
Mean weight on admission, kg	8.43	16.31	0.03†
Sex			
Female, n	29	24	0.709*
Male, n	25	24	
Mean baseline chloride, mmol/L	94.07	92.83	0.03†
Calculation of arginine dose			
Established dosing, n	2	12	0.002*
Other dosing, n	52	36	
Mean arginine dose, mEq/day	15.22	19.59	0.268†
Route of arginine administration			
Intravenous, n	14	32	<0.001*
Oral, n	39	16	
Frequency of arginine administration*			
Once	4	16	
Q 3 hr, n	4	0	
Q 6 hr, n	33	13	
Q 8 hr, n	4	7	
Q 12 hr, n	6	7	
Q 24 hr, n	2	3	
Mean time to resolution of hypochloremia and mean time to arginine discontinuation in patients whose hypochloremia did not resolve, hr	33.69	21.66	0.06†

* Chi-square.
† Independent *t*-test.

(range), respectively. The initial dose of arginine was 19.9 ± 34.28 (range) mEq/day independent of indication. The most common administration frequency for arginine was every 6 hours (n = 80, 45%), followed by a one-time arginine dose (n = 36, 20%) and every 8 hours (n = 28, 16%). Ninety-four arginine administrations were oral (53%) and 83 were intravenous (47%). Forty administrations utilized the established dosing method (23%) and the remaining 137 administrations (77%) utilized a provider determined method. Greater details on arginine dosing can be found in Table 2.

Data was analyzed separately for patients receiving treatment for hypochloremia (Table 3). This was also attempted for patients receiving arginine for metabolic alkalosis treatment (Table 4) but could not be completed successfully due to low sample size. As a result, pooled data are also presented (Tables 5 and 6). These pooled data consist of patients who received arginine for metabolic alkalosis alone as well as metabolic alkalosis combined with hypochloremia (Table 5) and who received arginine for hypochloremia alone as well as hypochloremia combined with metabolic alkalosis (Table 6).

Hypochloremia. One-hundred two of the arginine administrations were given to treat low serum chloride. Of these, 54 (53%) resulted in normalization of chloride levels. Fourteen administrations (14%) used the established dosing method, and of those, only 2 had normalization of chloride levels.

Hypercarbia. Fifteen arginine administrations were given to treat metabolic alkalosis. Of these, 11 (73%) resulted in normalization of bicarbonate levels. None of these administrations used the established method for dosing.

Hypochloremia and Hypercarbia. Sixty administrations of arginine were administered to treat both hypercarbia and hypochloremia. Of these, 26 resulted in normalization of chloride levels (43%), 48 in normalization of bicarbonate levels (80%), and 23 in normalization of both chloride and bicarbonate levels (38%). Six of these administrations to resolve metabolic alkalosis used the established dosing method (10%), and 5 of

Table 4. Comparison of Variables in Pediatric Patients with Resolved and Unresolved Metabolic Alkalosis Following Arginine Administration

Variable	Metabolic Alkalosis		p value
	Resolved	Unresolved	
Mean age on admission, yr	2.12	0.22	0.8232†
Mean weight, kg	11.51	4.69	0.186†
Sex			
Female, n	7	2	1‡
Male, n	4	2	
Mean baseline bicarbonate, mEq/L	35.82	35.75	0.942†
Calculation of arginine dosing			
Established, n	0	0	1‡
Other, n	11	4	
Mean arginine dose, mEq/day	20.1	5.5	0.267†
Route of administration			
Intravenous, n	7	2	1‡
Oral, n	4	2	
Frequency of arginine administration			
Once	13	3	
Q 3 hr, n	3	1	
Q 6 hr, n	29	4	
Q 8 hr, n	12	3	
Q 12 hr, n	4	1	
Q 24 hr, n	1	1	
Mean time to resolution of metabolic alkalosis (i.e., serum bicarbonate) and mean time to arginine discontinuation in patients whose alkalosis did not resolve, hr	21.47	5.2	0.017†

* Chi-square.
† Independent *t*-test.
‡ Fisher's exact test.

these (83%) resulted in resolution of bicarbonate levels. Eleven administrations (18%) used the established dosing method to resolve hypochloremia, and of these, 3 (27%) resulted in normalization of chloride levels.

Chloride levels took an average of 33.69 ± 32.54 hours to resolve (range 1.02–159.6 hours), whereas bicarbonate levels took an average of 21.47 ± 16.64 hours to resolve (range 0.77–57.33 hours). The mean oral daily dose was 25 mEq/day and the mean intravenous daily dose was 14.1 mEq/day. Doses were given on varying schedules, from one time doses to administration every three hours. Some patients received dosing within the recommendations by Martin and Matzke,[14] while other patients received dosing per provider preference. This dose was commonly 1 mEq/kg, but a variety of dosing regimens existed. The frequency and timing of laboratory blood draws varied by patient. No hypersensitivity to arginine or discontinuation of arginine secondary to adverse events was reported.

Chi-square analysis using pooled data revealed that utilization of the established method of arginine less frequently resulted in normalization of chloride levels compared with alternative methods ($p = 0.001$, Table 5). Fisher's exact test showed no significance in a similar comparison of normalization of bicarbonate levels ($p = 1.000$). Oral administration resulted in 63% of administrations achieving chloride level normalization compared with 37% of intravenous administrations ($p < 0.001$), but no such difference was seen for normalization of bicarbonate levels ($p = 0.926$).

In examining pooled data, chloride levels that normalized had a statistically significantly higher baseline chloride level (93.83 mmol/L vs. 82.25 mmol/L, $p = 0.001$) and had a greater time to normalization compared to the mean time to medication discontinuation where chloride levels did not normalize (36 vs. 20 hours, $p = 0.002$). There was no statistically significant difference between the mean dose of arginine administered be-

Table 5. Comparison of Variables in Pediatric Patients with Resolved and Unresolved Hypochloremia Following Arginine Administration—Pooled Data

Chi-square			
Chloride	**Resolved**	**Did Not Resolve**	**p value**
Established dosing, n	5	20	0.001*
Other dosing, n	76	61	
IV, n	30	55	<0.001*
PO, n	51	26	
Female, n	42	32	0.115*
Male, n	39	49	
Independent *T* test			
Chloride		**Value**	**p value**
Mean dose of patients who resolved, mEq/day		17	0.227†
Mean dose of patients who did not resolve, mEq/day		23.5	
Mean time to resolution of patients who resolved, hr		36	0.002†
Mean time to medication discontinuation in patients who did not resolve, hr		20	
Mean baseline chloride of patients who resolved, mmol/L		93.83	0.001†
Mean baseline chloride of patients who did not resolve, mmol/L		82.25	

* Chi-square.
† Independent *t*-test.

tween normalized and non-normalized chloride levels (p = 0.227). None of these parameters were statistically significant in the group with abnormal bicarbonate levels (Table 6), except that bicarbonate levels that normalized had a statistically significantly lower baseline bicarbonate compared with those whose bicarbonate did not resolve (36 mmol/L vs. 38 mmol/L, p = 0.005). Differences between administration frequencies for both indications could not be calculated due to small sample size.

In looking only at the administrations that resulted in normalization, there was no statistically significant difference between the average daily dose of arginine in comparing oral and intravenous administration (p = 0.363). However, the mean oral dose to normalizing chloride levels was statistically significantly higher than the mean intravenous dose (24.97 vs 11.47 mEq/day, p = 0.034).

Logistic regression analysis of pooled data showed no association between oral or intravenous administration and time to resolution of chloride levels (p = 0.144), though intravenous administration was favored in resolving bicarbonate levels (p < 0.001). Similarly, linear regression showed no association between the frequency with which arginine was administered and the time to resolution of chloride levels (p = 0.178) or bicarbonate levels (p = 0.091) (Table 7). This analysis also did not show an association between use of the established dosing method as compared with other dosing methods and normalization of chloride (p = 0.24) or bicarbonate levels (p = 0.426).

Examination of the percent of calculated daily dose as determined by Martin and Matzke[14] to resolve bicarbonate and chloride levels was also conducted. The median percent of calculated bicarbonate dose that resolved is 34.55% (25th–75th percentile, 25.33–43.38), and the median percent of calculated chloride dose that resolved is 59.38% (25th–75th percentile, 23.08–135.71).

Discussion

Our study showed that arginine is efficacious in resolving both hypochloremia and metabolic alkalosis in pediatric patients. Oral arginine administration of arginine was more effective than intravenous administration in normalization of chloride levels. Dosing methods other than that proposed by Martin and Matzke[14] were more effective in resolving hypochloremia.

The most favorable frequency of administration was every 6 hours, though there were not enough data points in some frequencies of administration to decisively conclude that this is the optimal dosing strategy.

Table 6. Comparison of Variables in Pediatric Patients with Resolved and Unresolved Metabolic Alkalosis Following Arginine Administration—Pooled Data

Chi-square			
Bicarbonate	**Resolved**	**Did Not Resolve**	**Chi-square value**
Established dosing, n	11	2	1.000‡
Other dosing, n	51	11	
IV, n	39	8	0.926*
PO, n	23	5	
Female, n	24	6	0.618*
Male, n	38	7	
Independent *T* test			
Bicarbonate		**Value**	**p value**
Mean dose of patients who resolved, mEq/day		20.1	0.18†
Mean dose of patients who did not resolve, mEq/day		40.0	
Mean time to resolution of patients who resolved, hr		23	0.368†
Mean time to medication discontinuation in patients who did not resolve, hr		15	
Mean baseline bicarbonate of patients who resolved, mmol/L		36	0.005†
Average baseline bicarbonate of patients who did not resolve, mmol/L		38	

* Chi-square.
† Independent *t*-test.
‡ Fisher's exact test.

Established studies do not recommend a frequency of administration of arginine or administration time for indications other than pituitary function tests.

The original dosing strategy for chloride correction utilizing arginine was extrapolated from case studies in adults in which intravenous hydrochloric acid was given to correct metabolic alkalosis.[9] In studies published since, the dosing strategy for resolving excess bicarbonate resulted in a lesser required hydrochloric acid dose than that of the chloride deficit method. As a result, previous case studies recommended and utilized replacement of 100% of the chloride deficit as compared with 50% replacement of the bicarbonate deficit.[10,14] This is in contrast to what is commonly found as a dosing recommendation in tertiary references but corroborates the results of this study, wherein we found that approximately 60% of the calculated chloride deficit is required to normalize hypochloremia, whereas 35% of the bicarbonate deficit is required to normalize metabolic alkalosis.

The limitations of this study include that it is a retrospective, single center trial with a small sample size. Due to the limitations in the sample size, it was difficult to account for additional factors (e.g., administration of electrolytes, mechanical ventilation) that could confound the results. This also made it difficult to analyze the effects of arginine administration on bicarbonate normalization alone. There is also no dosing protocol for arginine utilized at our institution, making comparisons between dosing strategies difficult.

Conclusions

Based on the results of our study, as well as previously published data, we conclude that arginine hydro-

Table 7. Logistic Regression Analysis of the Effect of Time to Resolution of Hypochloremia and Metabolic Alkalosis—Pooled Data

Variable	**p value**
Hypochloremia	
Established dosing vs. other dosing	0.24
Oral vs. intravenous administration	0.144
Frequency of administration	0.178
Bicarbonate	
Established dosing vs. other dosing	0.426
Oral vs. intravenous administration	<0.001
Frequency of administration	0.091

chloride is an effective method for improving metabolic alkalosis and hypochloremia. While optimal route and frequency of administration remain unclear, there is compelling evidence to show that current arginine dosing recommendations may underdose in the setting of hypochloremia and have potential to overdose in metabolic alkalosis. Our data suggest that administration of arginine using the established dosing method is no more effective than other methods. Further prospective study is warranted to validate these results.

ARTICLE INFORMATION

Affiliations School of Pharmacy (CMS, KAP) Loma Linda University, Loma Linda, California and College of Pharmacy (EAH) Marshall B. Ketchum University, Fullerton, California

Correspondence Caroline M. Sierra, PharmD; csierra@llu.edu

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Accepted August 13, 2017

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