

Evaluation of Failure to Thrive: Diagnostic Yield of Testing for Renal Tubular Acidosis

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ABSTRACT. *Background.* Failure to thrive (FTT) poses a diagnostic dilemma for pediatricians. The kidney disorder that is considered most often is renal tubular acidosis (RTA). However, the prevalence of RTA may be overestimated, leading to unnecessary referrals for subspecialty evaluation. Moreover, preliminary data suggest that venous blood gas (VBG) testing may provide a more accurate measurement of the serum bicarbonate concentration than routine biochemical testing.

Objective. 1) To compare the results of bicarbonate measurements by using VBG and routine clinical biochemistry methods under a variety of in vitro conditions; 2) to determine the frequency of RTA as a cause of FTT; and 3) to assess the utility of VBG measurement of serum bicarbonate in the clinical assessment of RTA.

Experimental Design and Methods. In blood samples collected from healthy volunteers, bicarbonate was measured by using a VBG apparatus and a clinical biochemistry analyzer under a variety of in vitro conditions including variation in time until sample processing (0–4 hours), variations in temperature (room temperature versus on ice), addition of sodium fluoride, or addition of heparin. A retrospective chart review was also performed of all children referred to the renal clinic for evaluation of FTT during the 5-year period of 1997 to 2002. The following data were collected for each case: demographic and clinical information and laboratory testing including serum bicarbonate determined by both routine biochemical testing and VBG analysis. Data are reported as mean \pm standard deviation.

Results. In the in vitro studies, VBG determination of bicarbonate concentration consistently yielded a value that was 3 to 6 mmol/L higher than routine biochemical analysis regardless of whether the sample was processed immediately or up to 4 hours later, maintained at room temperature or on ice until the measurement was performed, or the sample tube contained sodium fluoride or heparin. Thirty-six children were referred to exclude a renal etiology of FTT with a presumptive diagnosis of RTA in all cases. The patient group was comprised of 16 males and 20 females whose ages ranged from 4 to 156 months (mean: 27 ± 33 months). The serum bicarbonate

concentration determined by biochemical testing was 18 ± 4 mmol/L, whereas the bicarbonate level by VBG was 24 ± 3 mmol/L. The mean difference between the bicarbonate by VBG and bicarbonate by routine biochemistry measurements was 5.6 ± 4.4 . Only 1 child (2.8%) was confirmed to have RTA.

Conclusions. RTA is a rare renal cause of FTT in children. VBG determination of serum bicarbonate yielded a significantly higher value than the result obtained by routine biochemical testing under both in vitro and in vivo conditions. These data suggest that reliance on routine biochemical testing results in an overestimation of the importance of RTA as a cause of FTT. We recommend the use of a VBG determination of serum bicarbonate concentration for the evaluation of a child with FTT who is thought to have a metabolic acidosis. Adoption of this practice will reduce the number of children suspected of having RTA and decrease the need for referral to a nephrologist for further evaluation. *Pediatrics* 2003;112:e463–e466. URL: <http://www.pediatrics.org/cgi/content/full/112/6/e463>; failure to thrive, renal tubular acidosis, bicarbonate, venous blood gas.

ABBREVIATIONS. FTT, failure to thrive; RTA, renal tubular acidosis; VBG, venous blood gas; RBP, routine biochemistry panel.

Failure to thrive (FTT) is a common childhood problem that causes parental concern and poses a diagnostic dilemma for primary care pediatricians. FTT is caused by a wide range of diseases affecting every organ system.¹ One of the commonly suspected systems is the kidney, and the disorder most often considered is renal tubular acidosis (RTA). Although primary RTA is recognized to be a rare disease by pediatric nephrologists, referrals from general pediatricians to exclude RTA seem out of proportion to the incidence of the disease. Inaccuracies in the measurement of serum bicarbonate concentration may contribute to this problem.

Serum bicarbonate commonly is measured as part of a biochemistry panel. This method measures HCO_3^- as well as dissolved CO_2 and H_2CO_3 . The result is often reported as CO_2 or total CO_2 , but $\sim 99.8\%$ of the amount reported represents bicarbonate.² Thus, the CO_2 as reported on blood biochemistry panels is a measure of serum bicarbonate and regarded as such in clinical practice. Venous blood gases (VBGs) provide an estimate of bicarbonate derived by applying the Hendersen-Hasselbalch equation to the measurement of pH and pCO_2 in a hep-

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Received for publication Feb 3, 2003; accepted Aug 4, 2003.

This work was presented in part at the annual meeting of the Society for Pediatric Research, May 3, 2003, Seattle, WA.

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arinized, anaerobic venous blood sample. The quantitative relationship between these 2 measurements has never been assessed systematically.

Preliminary data collected in our laboratory suggest that VBG testing may provide a more accurate measurement of the serum bicarbonate concentration compared with routine biochemical testing. Therefore, we conducted this retrospective study 1) to compare the results of bicarbonate measurement by using VBG and routine biochemistry methods under a variety of in vitro conditions; 2) to determine the frequency of RTA as a cause of FTT; and 3) to assess the utility of VBG measurement of serum bicarbonate in the assessment of RTA. In this article, CO₂ as reported on a routine biochemistry panel (RBP) will be referred to as bicarbonate_{RBP}, and bicarbonate derived from VBGs will be referred to as bicarbonate_{VBG}.

EXPERIMENTAL DESIGN AND METHODS

In Vitro Studies

Blood was drawn from 7 healthy adult volunteers (3 males:4 females, 24 ± 2 years old). A sample was first drawn anaerobically into a heparinized tube for VBG analysis. The remaining blood was divided into a set of routine Vacutainer tubes and Vacutainer tubes containing sodium fluoride, an inhibitor of glycolysis. The tubes then were either kept in ice or at room temperature for 0, 2, or 4 hours and then analyzed for bicarbonate by routine biochemistry testing. In a second series of studies, blood was drawn from 5 healthy volunteers and divided into an anaerobic, heparinized syringe for VBG analysis and into 2 additional anaerobic syringes (1 heparinized and 1 nonheparinized) for routine biochemical testing. Finally, in a third series of experiments, blood was drawn from 5 healthy volunteers and placed into 2 routine nonanaerobic Vacutainer tubes (both containing heparin), and, after 30 minutes, a VBG determination of bicarbonate was performed by using 1 tube, and a routine biochemical determination of bicarbonate was performed with the second tube.

Clinical Review

A retrospective chart review was performed on all children referred to the Schneider Children's Hospital Nephrology Clinic for evaluation of FTT over the 5-year period of 1997 to 2002. The following demographic and clinical information was tabulated: age, gender, weight and height percentile, urine specific gravity and pH, blood urea nitrogen and serum creatinine concentrations, and serum bicarbonate_{RBP} and bicarbonate_{VBG}, as defined above.

The urinalysis was conducted by using the Multistix 8 SG reagent strips (Bayer Corporation, Elkhart, IL). The serum electrolytes, urea, and creatinine measurements were obtained by using the Olympus AU 2700 analyzer (Olympus America Inc., Irving, TX), and the VBG testing was conducted by using an Instrumentation Laboratory Synthesis 35 device (Instrumentation Laboratory, SpA-Viale Monza, Milano, Italy).

The data are reported as mean ± standard deviation. The difference between values was evaluated by using a paired *t* test or analysis of variance where appropriate and was considered significant if *P* < .05.

RESULTS

A series of studies was performed by using blood samples obtained from healthy volunteers. As summarized in Table 1, the bicarbonate_{VBG} was higher than the bicarbonate_{RBP} under all test conditions (*P* < .05). These conditions included storage of the biochemistry specimen at room temperature or on ice for 0 to 4 hours, the addition of heparin or sodium fluoride, or the presence of an air-blood interface.

Thirty-six children were referred to the Nephrology Clinic for evaluation of FTT with a presumptive

TABLE 1. VBG and Routine Biochemical Testing of Bicarbonate Concentration

Test Condition	Bicarbonate (mmol/L)
VBG	
Anaerobic	27.2 ± 0.5*
Nonanaerobic, 30 min	27.0 ± 0.9*
Routine biochemistry panel	
Whole blood, room temp., 0 hours	23.8 ± 0.3
Whole blood, room temp., 2 hours	22.9 ± 0.4
Whole blood, room temp., 4 hours	23.1 ± 0.5
Whole blood, room temp., heparin, 0 hours	22.6 ± 0.8
Whole blood, room temp., NaF, 0 hours	22.7 ± 0.5
Whole blood, room temp., NaF, 2 hours	22.3 ± 0.3
Whole blood, room temp., NaF, 4 hours	22.5 ± 0.6
Whole blood, on ice, 2 hours	22.4 ± 0.4
Whole blood, on ice, 4 hours	23.1 ± 0.3
Serum, room temp., 2 hours	22.6 ± 0.3
Serum, room temp., 4 hours	22.0 ± 0.6
Serum, on ice, 2 hours	21.3 ± 0.3
Serum, on ice, 4 hours	21.7 ± 0.6

Results are provided as mean ± standard deviation.

* *P* < .05 versus all routine biochemistry panel measurements of bicarbonate concentration.

diagnosis of RTA. The patient group included 16 males and 20 females and their ages ranged from 4 to 156 months (mean: 27 ± 33 months). The body weight of 18 (50%) patients was <5th percentile, but only 6 (17%) patients had a height that was <5th percentile. Moreover, only 5 (14%) children had both weight and height <5th percentile. The urine pH was 6.7 ± 0.2, and the specific gravity was 1.014 ± 0.003. The serum potassium was 4.7 ± 0.6 mmol/L, serum sodium was 139 ± 3 mmol/L, and the serum chloride was 106 ± 4 mmol/L. The serum creatinine, 0.4 ± 0.1 mg/dL, was normal in all children. The bicarbonate_{RBP} was 18 ± 4 mmol/L. In contrast, bicarbonate_{VBG} was 24 ± 3.0 mmol/L. The bicarbonate_{RBP} was normal in only 9 patients, whereas the bicarbonate_{VBG} was normal in 35 patients. The mean difference between the VBG and routine biochemistry serum bicarbonate measurements was 5.6 ± 4.4 mol/L (*P* < .0001). None of the children deemed normal, based on the bicarbonate_{VBG} measurement, required reevaluation for RTA or other kidney problems.

Of the 36 referrals, only 1 child (2.8%) was confirmed to have RTA. This patient presented at the age of 36 months with a history of persistent metabolic acidosis and weight loss beginning at 1 month of age. He was unable to breastfeed and was fed a soy-based formula. His weight was <5th percentile, and his height was at 5th percentile. The urine pH was 6. Both the serum bicarbonate_{RBP} and bicarbonate_{VBG} were low (11 and 13 mmol/L, respectively). The serum chloride was elevated (123 mmol/L), whereas the serum sodium and potassium concentrations were normal (140 and 5 mmol/L, respectively). Urinary excretion of calcium and citrate were not measured. He had a normal kidney function (serum creatinine: 0.4 mg/dL) and a normal renal ultrasound. He was started on sodium citrate supplement (Bicitra), 5 mL 3 times daily, providing ~3 mmol/kg per day of bicarbonate. After 2 weeks of treatment, he gained nearly 0.4 kg, and the bicarbon-

ate_{VBG} level rose to 22 mmol/L. This growth response was sustained over 27 months of follow-up in parallel with normalization of the bicarbonate_{VBG}.

DISCUSSION

The *in vitro* studies confirm that VBG testing consistently yields a higher bicarbonate value than simultaneous determinations performed by using a routine biochemical analyzer. The difference is unrelated to any delay in processing or glycolysis in routine biochemical specimens, collection of VBG samples on ice, addition of heparin to VBG samples, or the absence of air-blood interface in VBG specimens. It is possible that centrifugation of blood specimens to obtain serum for routine biochemical testing eliminates erythrocyte buffers and alters the equilibrium between bicarbonate and intracellular buffers.

There are 4 primary renal causes of FTT: 1) chronic renal failure; 2) nephrogenic diabetes insipidus; 3) hypophosphatemic rickets; and 4) RTA. Chronic renal failure is diagnosed on the basis of an elevated serum creatinine and antecedent history consistent with renal pathology. Diabetes insipidus is characterized by polyuria and inappropriately dilute urine.³ Hypophosphatemic rickets is an X-linked dominant disorder in which there is defective proximal tubular reabsorption of phosphate and impaired conversion of calcidiol to calcitriol. Affected patients present with bowing of the lower extremities related to weight-bearing at the age of walking.⁴ In contrast to these entities, RTA is marked by a paucity of clinical findings and is confirmed by the presence of a hyperchloremic normal anion gap acidosis. Because patients with RTA have a normal glomerular filtration rate, they usually have minimal symptoms.

There are 3 common types of RTA, each with its own distinctive features. Type 1 or distal RTA is caused by disturbances in any of a variety of steps involved in the distal renal acidification mechanism. This results in compromised hydrogen ion (H⁺) secretion and an inability to acidify the urine. Therefore, the urine pH is always high (>6.0), and the urine anion gap, a reflection of H⁺ secretion,⁵ is increased in the face of chronic metabolic acidosis. The individual abnormalities that can cause type 1 RTA include impaired H⁺ secretion secondary to reduced H⁺-ATPase activity, increased back diffusion of H⁺ across the renal epithelium, and inability to generate luminal electronegativity.⁶

Type 2 or proximal RTA is caused by a defective proximal tubular reabsorption of bicarbonate. Patients with this disorder have a decreased renal bicarbonate threshold, resulting in increased urinary losses of bicarbonate.⁷ However, the acidosis is self-limited, because the urinary bicarbonate leak stops once the plasma bicarbonate level falls below the renal threshold, which is usually ~15 to 18 mmol/L. The acidification mechanism in the distal nephron is preserved. Type 2 RTA is confirmed clinically by a high fractional urinary excretion of bicarbonate.

Type 4 RTA is a consequence of aldosterone deficiency or tubular resistance to the action of this hor-

mone. Because aldosterone promotes potassium and hydrogen ion secretion by the cortical collecting tubule, type 4 RTA results in metabolic acidosis and hyperkalemia.⁸ The metabolic acidosis results not only from impaired hydrogen ion secretion but also from decreased ammonia synthesis secondary to hyperkalemia.⁸ The serum potassium was normal in all of our cases excluding type 4 RTA. Nonetheless, despite the differences noted in the various forms of RTA, hyperchloremia and persistent metabolic acidosis are indispensable features.

In our group of patients, more than one third of the patients had both a weight and height ≥10th percentile for their age at the time of referral. Furthermore the weight of only 18 (50%) and the height of only 6 (17%) patients were <5th percentile. Only 1 patient had a low bicarbonate_{VBG}, and he represented the single, newly identified case of RTA, suggesting that in the evaluation of FTT, testing for RTA in particular may be premature in most cases. The diagnosis of RTA in this child was based on the presence of hyperchloremic metabolic acidosis, confirmation of hypobicarbonatemia on VBG testing, and normalization of growth after initiation of bicarbonate supplementation. In view of these findings, specialized testing such as stimulation of acid secretion after oral administration of furosemide or measurement of the urine-blood pCO₂ gradient was not performed. Consistent use of bicarbonate_{VBG} measurements for screening and follow-up may enable the diagnosis of RTA to be made without the need to conduct these more costly tests. In any event, we suggest that they should only be conducted to confirm the presence of RTA in children with an abnormally low bicarbonate_{VBG} level.

The principal finding of this study is the consistently higher level of serum bicarbonate concentration based on VBG versus routine biochemical testing. This may reflect the presence of erythrocyte buffers in the whole-blood VBG sample compared with the serum specimen using automated biochemical analyzers. Based on the data in this report, we propose that bicarbonate_{VBG} is a more accurate measurement of bicarbonate than bicarbonate_{RBP}. We acknowledge that this is a novel suggestion, but it is supported by the following observations.

1. In this patient population, referred because they had a low bicarbonate_{RBP}, the majority (30 of 36) had normal linear growth. Because chronic acidosis impairs growth, the subsequent finding that those patients had a normal bicarbonate_{VBG} was consistent with their condition. We consider the earlier finding of a low bicarbonate_{RBP} incompatible with the patients' health status in the absence of an acute illness that might have caused transient acidosis.
2. There was a discrepancy in bicarbonate_{RBP} in 9 children with low values obtained before referral and normal levels in our clinic. This suggests that there is considerable variability in bicarbonate_{RBP} determinations, which undermines its validity as a screen for metabolic acidosis.

3. The significant difference between bicarbonate_{VBG} and bicarbonate_{RBP} was similar in magnitude in both the clinical and in vitro studies.
4. The determination of bicarbonate_{RBP} often yielded values that were below or just at the lower limit of normal in the in vitro testing of healthy adult volunteers.
5. None of the children considered normal based on the bicarbonate_{VBG} subsequently required reevaluation for a renal cause of FTT.

Our findings suggest that the presence of a low serum bicarbonate concentration on routine biochemistry testing does not correctly indicate the presence of hyperchloremic metabolic acidosis. Moreover, this test is not a reliable screen for metabolic acidosis when RTA is under consideration and should be replaced by the bicarbonate_{VBG}, which provides a more accurate measurement of the serum bicarbonate concentration. Performance of a VBG determination of serum bicarbonate concentration requires no special procedure or equipment. However, this test is not often performed in community laboratories. Although it may be a nuisance to locate a hospital laboratory where the bicarbonate_{VBG} determination can be performed, we suggest that this inconvenience is outweighed by the benefit of obtaining an accurate test result and avoiding the need for further pediatric nephrology evaluation.

Isolated RTA is recognized to be a rare entity by pediatric nephrologists. Nonetheless, it is frequently invoked as a cause of FTT by general pediatricians prompting referral for a subspecialty renal evaluation. Our results suggest that use of routine biochemical methods to measure serum bicarbonate concentration compounds this error and leads to unnecessary referral to exclude the diagnosis of RTA.

CONCLUSIONS

RTA is a rare renal cause of FTT in children. The diagnosis of RTA by the primary care physician was

confirmed in <5% of patients referred to a nephrology clinic. In addition, VBG determination of serum bicarbonate concentration is significantly higher than the result obtained by routine biochemical testing and is a more accurate measurement of acid-base status. This suggests that reliance on routine biochemical testing results in an overestimation of the prevalence of RTA as a cause of FTT for bicarbonate concentration based on these findings. We recommend routine use of VBG testing for determination of serum bicarbonate concentration in any child with FTT suspected of having a metabolic acidosis. It is likely that this practice will greatly decrease the number of children suspected of having RTA and will avoid unnecessary referrals for renal evaluation.

ACKNOWLEDGMENTS

Olanrewaju Adedoyin is recipient of a Fellowship Award from the International Society of Nephrology.

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Pediatrics 2003;112:e463

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