Original bin widths

Statistically optimized bin widths

Fig. 1. Visual comparison of frequency distributions (A–D) and ROC curves (E, F) with original and optimized bin widths.

(A) Erythrocyte mean corpuscular hemoglobin (MCH) distributions in 88 healthy controls (upper bars) and in 88 patients with iron-deficiency anemia (lower bars); (C) erythrocyte count values from the same subjects (data from ref. 6). (B and D) The same data as in A and C, respectively, after statistical bin width optimization; thus does not affect the bin width (1 pg) for MCH, but increases that of erythrocyte count from 0.01 × 10¹²/L to 0.13 × 10¹²/L. Y-axis in A–D is the bin frequency. (E) The ROC curves for panels A and C; (F) ROC curves for panels B and D. The area under the curve for MCH (curves A and B) is 0.9236 (SE 0.0220). For erythrocyte counts, the area under the curve before bin width optimization (curve C) is 0.8246 (SE 0.0319); after bin width optimization (curve D), it is 0.8221 (SE 0.0323).

d-Lactic Acidosis in Patients with Short Bowel Syndrome

To the Editor:

I read with interest the article by Bongaerts et al. regarding d-lactic acidemia and aciduria in pediatric and adult patients with short bowel syndrome (1). Peace and I have previously reported our long-term experience with monitoring of d-lactic acidosis in a child with short bowel syndrome (2). Although Bongaerts et al. indicated that food consumption affected d-lactate production in those patients, they did not provide details of the feeding regimens utilized. It would be helpful if the amount of carbohydrate (g/kg body weight per day) provided enterally was reported,

References

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Editor’s Note: The author offers, upon request to the above address, free use of the program for a one-month trial; after that period, a registration fee is expected. The program runs under Microsoft Windows (a trademark of Microsoft Corporation).

depends only on the number of observations and their dispersion. If the standard deviation of the distribution is very high, the formula uses the nonparametric quartile limits instead of standard deviation.

This formula has been included in a computer program GraphROC for Windows, which is software Poola and I have developed for estimating clinical characteristics of laboratory tests (5). In the program, frequency histograms can be displayed by using either original or calculated bin widths. Optimal decision limits can be estimated by using simultaneous presentation of both health and disease-related distributions as well as sensitivity, specificity, and efficiency curves. The ROC curves can be drawn by using all possible cutoff limits, but the program also includes an optional possibility of using the statistically calculated standardized bin width in the display of the ROC curve and calculation of the area under the curve. These features facilitate test comparison by use of frequency histograms and ROC curves (e.g., see Fig. 1) in a way that is independent of data-rounding effects.
and if there was any evidence of malabsorption (stool pH, reducing substance). Many centers utilize continuous enteral drip feeds so that carbohydrate loads to the intestine and malabsorption are minimized in patients with short bowel syndrome. Although the details are not specifically elaborated, my impression is that the authors fed their short bowel patients with bolus feeds of a normal caloric diet enriched with carbohydrates and protein with a normal or slightly reduced fat content. Certainly, bolus feeds in such patients will provide increased opportunity for malabsorption of carbohydrate and d-lactate production. The time-related lactate excretion and serum lactate values observed in their patients may merely reflect the periods of feeding, fasting, and malabsorption. In our patient who received continuous enteral drip feedings and was monitored for d-lactic acidosis long-term, we found that d-lactate concentrations and neurological symptoms correlated nicely. Other reports have suggested that abnormal concentrations of phenylacetic acid and p-hydroxyphenylacetic acid found in the urine of these short bowel patients (9–11) perhaps contribute to the neurological symptoms observed. Did the authors find evidence of these phenolic acids in their specimens as part of the analysis for organic acids?

References

Philip Rosenthal

The authors of the article referred to respond:

To the Editor:

Management of short bowel syndrome is a multistage process, beginning with total parenteral nutrition, and via continuous enteral (partially) elemental feeding ending with bolus feeding (1). Just as described by Rosenthal and Pesce (2), our short bowel (SB) children (CH-1 and CH-2; see ref. 3) after resection initially received total parenteral nutrition and subsequently continuous enteral nutrition. Later, when they had recovered sufficiently, they were allowed bolus feeding. The eating pattern consisted of three main meals during the day alternated with smaller snacks, guided by their appetite. As for the composition of the diet, both children were on a lactose-free diet for the first 2 years of life, but CH-2 remained so because of clinical lactose intolerance. The other child started to tolerate lactose as she grew older. Lactose malabsorption and intolerance was at times confirmed by means of breath hydrogen testing after intake of lactose or milk, combined with analysis of pH and reducing substances in freshly produced liquid stools, if obtained during the test. In these children’s diet, carbohydrates other than lactose were not restricted and the total carbohydrate content was ~55% of their energy intake, based on recommended dietary allowances for Dutch children. Our SB adults (3) did not receive enteral drips, but liberal enteral bolus feeding (≥6 times/day, including three main meals). They had a normal caloric diet (1800–2700 cal/day) of ~50% carbohydrates, but were lactose-restricted (3). Four of the six received additional parenteral nutrition for 10 h during the night. Stool pH was not routinely checked, but was slightly acid at testing.

Because in SB patients ~80% of the small bowel has been resected, a significant percentage of nutrient uptake capacity has been lost. Thus, after resection, more nutrients will be available intestinally for bacterial growth than in nonresected persons. Simultaneously, the total percentage of calories absorbed through drip feeding may be greater than that tolerated with bolus feedings because of continuous saturation of transport carriers in the small intestine (1). Nevertheless, the bacterial fermentation product, d-lactate, was detected in blood and urine during continuous-drip feeding (2) as well as during bolus feeding (3). This means that under both circumstances d-lactate-producing flora emerges; therefore, most, if not all, SB patients will have some d-lactic acidemia. Every day after the last meal (i.e., ordinarily, during the night), d-lactate production will stop, and thus also d-lactate accumulation in blood, but the clearing might go on until the first meal next morning. We are fully aware (3) that the circadian rhythm in d-lactic acidemia and aciduria in these patients reflects probably the bolus feeding pattern followed. As for the children, despite the occurrence of acidic episodes associated with hyperventilation, especially when they were younger, we still preferred bolus feeding because it allowed a normal lifestyle and was generally well-tolerated. In SB children, d-lactate produced during continuous enteral drip infusion (2) will also accumulate and give rise to d-lactic acidemia, unless intestinal d-lactate production is in equilibrium with d-lactate clearing. This makes the benefit of using overnight drip infusion feeding to avoid acidosis somewhat questionable.

Part of our research in short bowel syndrome also involves the study of (a) the bacterial fecal flora, (b) the presence of metabolites from bacterial origin in blood and urine of SB patients (manuscripts submitted and in preparation, respectively), and (c) the origin of neurological symptoms. Gas-chromatographic analysis of organic acids yielded not only ample information on lactate (2), but also on other metabolites such as 1,3-propanediol, 3-hydroxypropionic acid, and various phenolic acids. So far, evidence is lacking that only one of these compounds is responsible for creating the neurological symptoms occasionally observed in SB patients; however, it is not excluded that they may contribute to the occurrence of these symptoms. In addition, we could not demonstrate a clear relation between encephalopathy (disorientation and loss of higher cortical functions) and serum concentrations of d-lactate. Rosenthal and Pesce reported that d-lactate concentrations and neurological symptoms correlated nicely, but treatment with sodium bicarbonate temporarily corrected only the acidosis, and not the neurological symptoms (2). According to Karton et al., cortical dysfunction did not occur when serum d-lactate concentrations were greatest (4). Finally, regarding our patients, the following events are worth mentioning. When CH-2 was 2 years old and entirely on enteral nutrition, she de-
developed a sudden difficulty in walking and a disturbed gait, which happened to be due to a carnitine deficiency; neurological symptoms resolved after adequate supplementation. Shortly before turning 4 years of age, CH-1 had to be admitted for a severe metabolic acidosis (pH 7.22), accompanied by lethargy, dysarthria, and ataxia. An 80-mL urine sample collected soon after admission demonstrated an extremely high D-lactate excretion, 40 000 mmol/mol creatinine, whereas L-lactate excretion was only 400 mmol/mol creatinine. Because neurological symptoms and acidosis resolved after administration of an oral prokinetic (cisapride) and a phosphate enema, we assume that intestinal stasis and the resulting excessive fermentation precipitated the metabolic acidosis.

References

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Snack Crackers Yield Opiate-Positive Urine

To the Editor:

With the prevalent use of urine screening to give an indication of drug abuse, the ingestion of food products that give rise to opiates in the urine poses a significant problem. Instances of opiate-positive urine samples resulting from the ingestion of poppy seed-containing baked goods have been well documented in the scientific literature (1-6). The Department of Defense has addressed this problem in their drug monitoring programs by setting urine opiate confirmation cutoff concentrations so high that positive results from the ingestion of poppy seeds in baked goods are unlikely (morphine cutoff = 4 mg/L, codeine cutoff = 2 mg/L) (2). However, the National Institute on Drug Abuse (NIDA) continues to maintain the lower confirmation cutoff value of 0.30 mg/L, making interpretation of results more difficult as to whether illicit use of opiates has occurred.

A young woman on federal probation contacted our laboratory alleging her opiate-positive urine was the result of ingesting one-half box of poppy seed-containing “Sociables” snack crackers (Nabisco Foods, East Hanover, NJ) ~2 h before a mandated urine screening. After a review of the scientific literature, we found no instances of opiate-positive urine resulting from commercially available snack crackers and, therefore believed the scenario to be unlikely. However, to test the allegation of the probationer, two male volunteers with no history of opiate use each ingested one-half box (115 g) of Sociables snack crackers over a 30-min period. A preingestion urine specimen and all postingestion urine specimens collected in the next 27 h were assayed for opiates by Emit-st (Syva Co., Palo Alto, CA) by the manufacturer’s protocol. The Syva-supplied calibrator at 0.30 mg/L was used as the cutoff for a presumptive positive.

Morphine and codeine concentrations in the urines were isolated by liquid/liquid extraction and quantitated by selected-ion gas chromatography-mass spectrometry (GC-MS) on a Hewlett-Packard (Palo Alto, CA) 5970 GC-MS system. Full-scan confirmation of morphine was obtained in samples from each volunteer.

Emit-st testing showed positive urine opiate results for the first and second postingestion voids for each volunteer, collected ~5 and 9 h postingestion. Results for subsequent voids were below the GC-MS cutoff (0.30 mg/L), but Emit-st values remained above the preingestion values of both volunteers for 26 h.

The GC-MS quantitations (Fig. 1) show morphine concentrations of 0.28 and 0.29 mg/L for the first and second voids, respectively, for volunteer 1. Volunteer 2 showed morphine concentrations of 0.32 and 0.17 mg/L for the first and second voids, respectively. The GC-MS data generally followed the results obtained from the Emit-st testing. Codeine was detected in one specimen from volunteer 1 at a concentration of <0.10 mg/L.

We also assayed the snack crackers for opiate content by GC-MS. The total morphine concentration was 2.2 μg/g of cracker. Ingestion of 115 g of snack crackers would include 256 μg of morphine. Concentrations of morphine per gram of poppy seed have been reported to range from 1.5 to 963 μg/g in seeds of various origins (1). In