

Lactulose Interferes in the Alkaline Picrate Assay for Creatinine

David E. Bruns

Errors of more than 10 mg/L in measured serum creatinine concentrations were encountered for an azotemic patient who was given lactulose orally. The magnitude of the apparent error fluctuated with the dose of lactulose. Additions of lactulose to serum produced a linear increase in the creatinine measured by each of two automated methods that involve use of the alkaline picrate (Jaffé) reaction. A lactulose concentration of 100 g/L produced positive interferences of 30 and 65 mg/L in kinetic (Beckman Astra) and continuous-flow (Technicon SMAC) assays, respectively, but caused no problem in an enzymatic assay for creatinine. The results of creatinine assays must be interpreted with caution in patients treated with lactulose.

Additional Keyphrases: analytical error · azotemia · enzymic method compared · osmolality

Among the substances interfering with alkaline picrate methods for measurement of creatinine (1), at least one, fructose (2), is a simple sugar. I describe here an interference from lactulose, a sugar that is not metabolized in humans and is used in the treatment of hepatic coma (3).

Case Report

In a 45-year-old black female alcoholic being treated with oral lactulose for hepatic encephalopathy, progressive azotemia of undetermined etiology developed during the first week of hospitalization (Figure 1). Serum creatinine results obtained with the Beckman Astra and Technicon SMAC differed by 8 to 10 mg/L (Figure 1) during the second week of lactulose therapy, whereas the serum urea concentrations measured with the two instruments showed no such discrepancy. Lactulose administration was discontinued on day 13, and the discrepancy between the creatinine measurements in the two instruments rapidly decreased, being only 1 mg/L on day 15. Re-institution of lactulose again was accompanied by creatinine results that were discrepant by as much as 9 mg/L during a period when the serum creatinine and serum urea were decreasing. On day 20, the lactulose dose was decreased to <100 g/d and the discrepancy between SMAC and Astra results decreased to 1-2 mg/L (Figure 1).

Later in the patient's hospital course, a second episode of azotemia occurred, and treatment with lactulose produced a similar pattern for creatinine determination discrepancies (not shown).

Materials and Methods

Reagents for enzymatic assay (4) of creatinine (bmc/Biodynamics, Indianapolis, IN; cat. no. 166413) were used according to the manufacturer's directions. Pharmaceutical preparations of lactulose (10 g/15 mL) were obtained from the hospital pharmacy; information from the supplier indicated that these preparations contained <220 g of galactose,

120 g of lactose, and 120 g of other sugars per kilogram, and contained orange coloring and flavor, water, and NaOH to adjust pH. Lactulose (>99% stated purity) was purchased from Alltech, Deerfield, IL 60015.

Serum osmolality was measured by freezing-point depression, and osmolality gaps were calculated according to the formula of Dorwart and Chalmers (5). Ethanol was measured by an alcohol dehydrogenase method (*aca*; DuPont, Wilmington, DE).

Results

The discrepant creatinine results from the Astra and SMAC did not appear to be caused by any of the common sources of error in creatinine measurement. Tests for ketones were negative in both serum and urine. Although the patient was hyperbilirubinemic (21-47 mg/L), serum samples from other patients who had similar bilirubin concentrations yielded creatinine results that were indistinguishable by the two methods.

On the twenty-first day of hospitalization, measurement of the patient's serum creatinine by a coupled enzymatic assay showed 9 mg/L, compared with 10 mg/L by the Astra and 16 mg/L by the SMAC. Urine creatinine concentrations were 1.39 and 1.37 g/L by the enzymatic and Astra methods, respectively.

Adding pure lactulose to serum had no effect on the measured urea, but produced a positive interference in both the SMAC and Astra methods for creatinine, with the interference being greater for the SMAC results (Figure 2). The pharmaceutical preparation of lactulose interfered more than did pure lactulose. A nominal 100 g/L (about 300 mmol/L) solution of the pharmaceutical lactulose produced an apparent creatinine result of 104 mg/L as measured in the SMAC, vs about 65 mg/L with the pure lactulose. At test concentrations of 30 mmol/L, the interference from pure lactulose was similar to that for fructose, whereas galactose did not interfere at all.

A lactulose interference of 10 mg/L in SMAC-measured creatinine, as was seen in the patient (Figure 1), required a lactulose concentration of about 10 g/L (Figure 2), or 30

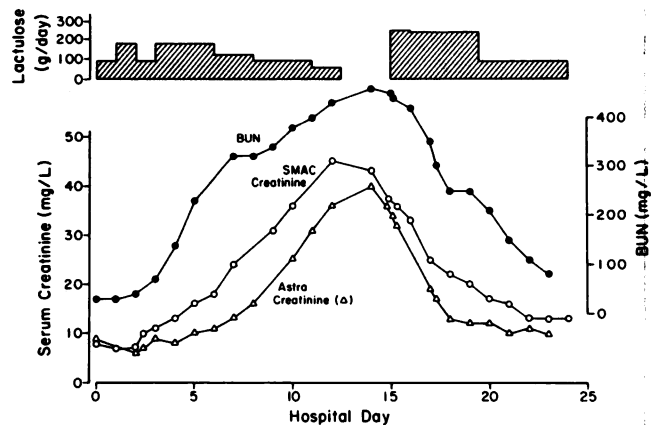


Fig. 1. Dose of lactulose (upper panel) and measured concentrations of apparent creatinine and urea (BUN) in serum

Department of Pathology, University of Virginia School of Medicine, Charlottesville, VA 22908.

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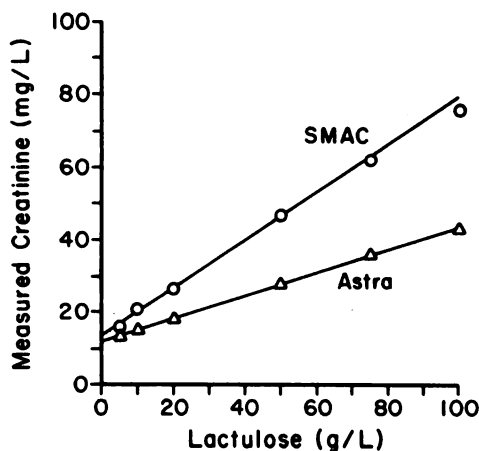


Fig. 2. Effect of added lactulose (99% purity) on measured creatinine in pooled serum

Each point represents one measurement. The y -intercepts reflect endogenous creatinine. Regression analysis yielded, for Astra, intercept = 11.7 ± 0.3 , slope = 0.32 ± 0.005 , $r = 0.9995$, SEE = 0.4. For SMAC these values were 14.2 ± 0.9 , 0.63 ± 0.02 , 0.9987, and 1.4, respectively.

mmol/L, a lactulose concentration expected to increase serum osmolality by about 30 mOsm/kg. The serum osmolality in the patient described here was 330 mOsm/kg on the tenth hospital day, whereas the calculated osmolality (5) was 298 mOsm/kg. The patient's osmolality gap, 32 mOsm/kg, thus was consistent with the presence of enough lactulose to produce the observed interference in the measurement of creatinine.

Discussion

These findings suggest that lactulose is absorbed from the intestine and interferes in measurements of serum creatinine by the alkaline picrate (Jaffé) method. The dialysis step used in the SMAC does not obviate the interference, but it is less marked in the kinetic Jaffé assay (Astra).

Lactulose is widely used in the treatment of hyperammonemia (3). After oral administration, the disaccharide is poorly absorbed from the human intestine, moving on to the colon, where it is degraded by the bacteria. The metabolism of lactulose by the bacteria leads to acidification of the colonic lumen and facilitates the removal of NH_4^+ .

Although commonly considered to be "non-absorbable" in the human gastrointestinal tract, some lactulose is in fact absorbed (6, 7). Absorption of lactulose has been demonstrated, e.g., from the human mouth and from rat small intestine (6). Indeed, Laker and Menzies (7) exploited lactulose absorption as an indicator of intestinal permeability and demonstrated its renal excretion. The peak concentration of lactulose in plasma was 24 mg/L after ingestion of 10 g of lactulose (7). Our patient received 180 g, almost 20 times as much, daily for several days. Her estimated peak plasma lactulose of 10 g/L, in the presence of renal impairment, appears to be consistent with the report of Laker and Menzies (7).

Evidently, absorption of lactulose produces a hyperosmolar state and an artifactual increase in serum creatinine, mimicking pre-renal azotemia. An increase of creatinine in serum of a patient with hepatic coma (the type of patient treated with lactulose) also suggests the onset of a hepatorenal syndrome. For these reasons, the artifactual increase of serum creatinine may be especially misleading. Alternative methods for creatinine measurement must be considered in patients who are undergoing treatment with lactulose.

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