False-Positive Ketostix in a Diabetic on Antihypertensive Therapy

To the Editor:

A diabetic patient who recently presented at our diabetic clinic reported frequent positive results for ketones when she tested her urine with Ames' Keto-Diastix, and that results varied even within-day.

At the clinic, the patient's blood sugar concentration was 10.0 mmol/L (fasting range 3.0-5.8 mmol/L). Her urine was positive for ketones ("small" = 2.5 mmol/L) with Keto-Diastix—and also with the Boehringer Combirest test strip. With an enzymatic β-hydroxybutyrate kit (Sigma Diagnostics) the β-hydroxybutyrate concentration in serum was 0.08 mmol/L (range 0-0.42 mmol/L) and <0.02 mmol/L in the urine.

Drug interference was suspected, and the patient was found to be taking several prescribed medications. Aqueous solutions of these drugs, tested with Keto-Diastix, revealed that the antihypertensive drug captopril gives a positive reading ("trace" = 0.5 mmol/L) for ketones at a concentration of 25 mg/L (0.12 mmol/L). By comparison, β-hydroxybutyrate at a concentration of 0.5 mmol/L gives an equivalent result; i.e., Keto-Diastix is four times as sensitive to captopril as to β-hydroxybutyrate.

Captopril (5-3-mercapto-2-methylpropanoyl-L-proline; Capoten, Squibb) (Figure 1) is an orally active inhibitor of angiotensin-converting enzyme. After oral administration, captopril is rapidly absorbed, with peak concentrations in blood reached in 30 to 90 min. The drug's half-life is about 2 h, and renal excretion is rapid, with about 40% appearing in the urine unchanged (1).

The patient was on a captopril dosage of 50 mg three times daily. On further enquiry she reported that her first morning urine was usually negative for ketones; that a mid-morning specimen, collected about 2 h after taking her medication, was often positive ("trace, "small"); and that a specimen tested much later (just before the next dose) usually yielded a negative result. If we assume that 40% of her 50-mg dose is excreted unchanged during 3-4 h in a urine volume of 200-300 mL, the concentration of captopril in her urine would be about 65-100 mg/L. Thus the pharmacokinetics of captopril and her dosage regimen together account for the results she observed.

As to the mechanism of interference with the nitroprusside reagent in the test strip, it is probable that the keto group of captopril may be reacting. We did not test metabolites of captopril for a reaction. We are not aware of a previous report of this interference and are surprised that false-positives with captopril are not encountered more often, because this drug is a popular antihypertensive.

Reference

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Fig. 1. Structural formula of captopril

Fig. 1. DLL (expressed as µg digoxin equivalents per liter) measured in the 10 patients

Endogenous Digoxin-like Immunoreactive Substances Eliminated from Serum Samples from Patients with Liver Disease by the EMIT Column Digoxin Assay

To the Editor:

Skogen et al. (1) evaluated the new EMIT Digoxin Column Assay (Syva Co., Palo Alto, CA), as adapted to the Co-bas-Bio centrifugal analyzer (Roche Diagnostics, Nutley, NJ). They compared the sensitivity of this assay to interference by digoxin-like immunoreactive substances (DLIS) with four other methodologically distinct digoxin immunoassays. They looked at DLIS interference with measurement of serum digoxin in patients with renal failure, pregnant women, and newborns and found that the EMIT assay eliminated or markedly decreased the incidence of false-positive digoxin results in these three groups of patients.

Previous studies have also demonstrated increased concentrations of DLIS in the serum of patients with liver disease (2). We therefore have investigated such patients for DLIS interference in this assay.

We compared results by the EMIT assay, as previously described (1), with the "NML Digi-Tab RIA" method (Organon Teknika Corp., Irving, TX). In the latter we used two different lots of digoxin antisera: NML antisemum lot DB-157, which has been described previously (3) as having high cross-reactivity with DLIS, and NML antisemum lot 04-058, which has lower cross-reactivity. For this study, we investigated 10 patients with liver disease, for all of whom we had data on total-bilirubin concentrations (mean 80 µmol/L, range 84-226 µmol/L). These patients had normal renal function and were not receiving digoxin therapy.

DLIS concentrations in these patients are presented in Figure 1. The DLIS