Tabolites of 1.2, 1.2, and 0.6 g/L, respectively. These icodextrin metabolite concentrations were reported to be the maximum reachable concentrations in vivo (2).

From each sample, 100 μL was centrifuged and analyzed on a Hitachi 911 with a plasma glucose dehydrogenase (GDH) method (Boehringer Mannheim). The whole blood samples were analyzed using an EML 105 with a GOD membrane method (Radiometer), a Chiron 865 with a GOD membrane method accompanied by a glucose reference electrode, and bedside glucose analyzers: Accutrend Sensor with a bioamperometric GDH method (Boehringer Mannheim), Glucocard Memory with a bioamperometric GOD method (Menarini Diagnostics), Glucotouch with a colorimetric GOD method (Lifescan, Johnson & Johnson), One Touch Profile with a colorimetric GOD method (Lifescan), One Touch II with a colorimetric GOD method (Lifescan), and Precision with a GOD method (Medisense). The results of the samples containing icodextrin metabolites were compared with the blank sample and expressed as a mean difference. Interference was defined as a mean difference >0.5 mmol/L (Table 1).

The icodextrin metabolites showed no interference in glucose measurements by the Hitachi 911 and the Chiron 865 analyzer. The EML 105 system showed a positive interference from maltose but no interference from maltotriose or maltotetraose. The bedside glucose analyzer Accutrend Sensor showed a considerable positive interference from all three icodextrin metabolites. The Glucocard Memory showed positive interference with maltose and maltotriose in one sample; for the other sample, it registered a result of “LO” (<2.2 mmol/L). The Glucotouch and the One Touch Profile showed no interference with any of the metabolites. The One Touch II showed a positive interference for maltotriose and maltotetraose. The Precision showed an interference with maltose in one sample and slight interference with maltotriose and maltotetraose in another sample. The interference was related to the concentration of the interferent, regardless of the glucose concentration of the sample.

In conclusion, the icodextrin metabolites may cause erroneously high glucose results, depending on the analysis system used. The clinically significant effect of interference by icodextrin metabolites is the potential risk of missing the diagnosis of hypoglycemia. Moreover, in diabetic patients undergoing icodextrin-CAPD therapy, the observed icodextrin metabolite interference may lead to unexplainable fluctuations in measured glucose.

### References

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**Influence of Uremic Toxins and Nonesterified Fatty Acids on Drug and Thyroid Hormone Binding in Serum**

To the Editor:

The findings of Takamura et al. (1) suggest that the furan fatty acid 3-carboxy-4-methyl-5-propyl-2-furan propionate (CMPF) is the major uremic toxin that inhibits albumin binding of the drug furosemide in chronic renal failure. These authors also invoke a potentially important cascade mechanism that can increase the unbound concentration of furosemide as a result of increased occupancy of...
drug binding sites on albumin by CMPF or oleate. To place these important observations in context, we wish to comment on the following: (a) the relevance of cascade effects in influencing the unbound concentrations of numerous other drugs such as aspirin and nonsteroidal antiinflammatory agents; (b) the importance of a similar cascade effect as a mechanism that can increase free thyroid hormone concentrations; and (c) the potential to overestimate the in vivo importance of apparent serum concentrations of nonesterified fatty acids (NEFAs) as direct or indirect inhibitors of hormone or drug binding.

Occupancy of albumin by CMPF (2) or oleate (3) has previously been shown to influence the unbound concentrations of drugs such as furosemide, meclofenamic acid, aspirin, mefenamic acid, and diflunisal, which in turn leads to an increase in the free thyroxine concentration by competitively inhibiting the binding of thyroxine to its specific binding globulin (3). By way of this cascade effect, free thyroid hormone concentrations can be influenced by substances that displace direct competitors from albumin without themselves having an intrinsic effect on thyroid hormone binding sites. Such cascade effects need to be considered with the numerous mechanisms that influence thyroid homeostasis in chronic renal failure (4) and other critical illnesses (5).

One observation that needs to be interpreted with caution is the finding by Takamura et al. (1) that a 6:1 molar excess of oleate over albumin (equivalent to a serum oleate concentration of 3–4 mmol/L CMPF at normal albumin concentrations), markedly increased the unbound fraction of furosemide in the presence of 0.3 mmol/L CMPF. Although such serum oleate concentrations may be found in sera from heparin-treated patients, they do not necessarily reflect the in vivo oleate concentration. Lipases released into the plasma in vivo in response to heparin can act on triglycerides in vitro during sample storage or incubation, thereby producing time- and temperature-dependent increases in the concentration of NEFAs to values much higher than those found in vivo (6, 7). In the presence of high triglyceride concentrations, this artifact may occur after doses of heparin as low as 10 units (8). Hence, the true in vivo influence of NEFAs on the binding of other ligands may be much less than that observed in vitro.

Takamura et al. (1) were able to account for almost all of the inhibition of furosemide binding on the basis of measurable uremic toxins such as CMPF without invoking any putative amplification of the effect by NEFAs. Nevertheless, the potential for a CMPF-oleate cascade effect is confirmed by the finding that 0.4 mmol/L CMPF produces a 35–40% increase in the unbound fraction of (14C)oleate (2), demonstrating in reverse the interaction documented by Takamura et al.

The concept of cascade effects on ligand binding in serum should be extended to include interactions between uremic toxins, drugs, and thyroid hormones. At high concentrations, NEFAs may also be involved, but the biologic importance of measured in vitro NEFA concentrations must be interpreted with caution.

It remains to be established whether the inhibition of thyroid hormone binding in critical illnesses that is observed in vitro (9) can be attributed to cascade effects that involve displacement of direct competitors from albumin, accentuated by heparin-induced in vitro generation of NEFAs. The interpretation of studies to elucidate these effects is critically influenced by the complex artifacts associated with sample dilution (10). In this respect, ultrafiltration of undiluted serum, as is used by Takamura et al, is likely to be the best analytical technique.

References


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Hb A2 in Subjects with Hb D

To the Editor:

Dr. Huisman’s paper on “Combinations of β chain abnormal hemoglobins with each other or with β-thalassemia determinants with known mutations: influence on phenotype” (1), was of great interest to us because Bahrain has a high prevalence of hemoglobinopathies (2). Monitoring with cation-exchange HPLC (BioRad Variant) was started in 1997, and 11 800 blood samples were screened in that year.