associated with erythrocytes may be less influenced by hematocrit than are serum analytes, specific studies on the distributions of individual analytes of interest are important. Such studies would be an essential prerequisite to the utilization of filter paper as a matrix for collecting blood samples for any quantitative analysis.

References

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False-Positive Serum Tricyclic Antidepressant Screen with Cyproheptadine

To the Editor:
A 14-year-old girl was admitted to our Emergency Department after an intentional ingestion of ~30 4-mg tablets of cyproheptadine (Periactin; Zenith Laboratories, Inc., Northvale, NJ). The patient was mentally confused, ataxic, and had a history of atypical migraine headaches. The toxicology requisition submitted with this patient's urine and blood specimens indicated signs/symptoms consistent with a hallucinogenic or anticholinergic pattern and current drug therapy consisting of cyproheptadine and Midrin (isomethypene mucate, dichloralphenazona, and acetaminophen; Duramed Pharmaceuticals, Cincinnati, OH). Cyproheptadine is an antihistamine and a serotonin antagonist with anticholinergic and sedative effects and, reportedly, calcium-channel blocking activity (1, 2). We performed a drug screen on both the urine and blood specimens submitted from this patient.

The results of all chemical spot tests for salicylates (urine and serum) (3), acetylmethionine (urine) (4), and phenothiazines (urine) (5); EMIT d.a.u (Syva Co., Palo Alto, CA) tests performed with the ETS instrument (Syva Co.); and EMIT st tests performed with the Qstat/Qst instrument system (Syva Co.) were negative except for the EMIT st assay for tricyclic antidepressants. Confirmatory testing by thin-layer chromatography (Toxi-Lab A; Toxi-Lab, Inc., Irvine, CA) and by gas chromatography–mass spectrometry (GC–MS; 5890 Series II gas chromatograph equipped with an Ultra-1 capillary column and a 5971 Mass Selective Detector, all from Hewlett-Packard, Palo Alto, CA) of a sample prepared from a Toxi-Tube A (Toxi-Lab, Inc.) extract of this patient's urine specimen did not confirm the presence of a tricyclic antidepressant. The GC–MS spectrum of the principal peak observed on the total ion chromatogram of this patient's urine extract was consistent, however, with the presence of cyproheptadine.

To determine the minimum concentration of cyproheptadine necessary to produce a reading equivalent to 200 $\mu$g/L for nortriptyline, the calibrator used in the EMIT st assay for tricyclic antidepressant assay, we tested 10 samples of pure cyproheptadine (Sigma Chemical Co., St. Louis, MO; cat. no. C-6022) prepared in drug-free serum at concentrations ranging from 100 to 1000 $\mu$g/L in 100 $\mu$L/L increments. All samples with apparent cyproheptadine concentration $\geq$400 $\mu$g/L were negative, while all samples with cyproheptadine $\geq$400 $\mu$g/L were positive. Quantitative GC–MS analysis of the sample containing cyproheptadine at 400 $\mu$g/L indicated the actual concentration was 390 $\mu$g/L.

After a single oral dose of cyproheptadine hydrochloride in healthy adults, $\sim$30% of the dose is excreted as conjugated glucuronid and sulfated metabolites in urine within 24 h, $\sim$50% within 48 h, and $\sim$65–75% within 6 days; the remainder of the dose is excreted in feces (1). Peak plasma concentrations of metabolites are detected $\sim$6–9 h after oral administration of parent drug (2).

To determine if therapeutic concentrations of cyproheptadine produce a positive response in the EMIT st serum tricyclic antidepressant assay, a healthy, drug-free volunteer ingested orally one 4-mg cyproheptadine tablet three times per day for 3 days. Serum obtained from blood samples taken from this volunteer before ingestion of the cyproheptadine; just before administration of the last dose; and 1, 2, and 4 h after the last dose of cyproheptadine were all negative when tested with the EMIT st tricyclic antidepressant assay.

Significant structural similarities (Figure 1) between cyproheptadine and tricyclic antidepressants (e.g., nortriptyline) most likely account for the cross-reactivity of cyproheptadine in the EMIT st serum tricyclic antidepressant assay.

Because immunoassays are typically affected by cross-reactants (6), knowledge of potential sources of false positives is important in the interpretation of drug-screening results and in the application of appropriate drugspecific therapy (7, 8). Fortunately, only concentrations of cyproheptadine $\geq$400 $\mu$g/L, an amount not likely to be observed in a therapeutic dosing regimen with cyproheptadine, provide a positive response in the EMIT st serum tricyclic antidepressant assay. Thus, cyproheptadine at $\geq$400 $\mu$g/L may be added to the current list of structurally related compounds that produce a positive result using this assay. Currently, the manufacturer of the EMIT st serum tricyclic antidepressant assay does not list cyproheptadine in their table of "Compounds Detected" by this assay (Syva Co., package insert, EMIT st serum tricyclic antidepressant assay, January 1987).

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Editor's note: A representative of the manufacturer has informed us that the interference by cyproheptadine has been confirmed and will be added to the package insert at its next revision.

book review


The "case method" is a classic form of instruction in medicine. This book makes an extremely valuable contribution by presenting a series of cases with appropriate history and sufficient background information to set the clinical tone, and subsequently introducing the laboratory information for evaluation and differential diagnostic merit. The contributors are an outstanding group of well-known and authoritative individuals. Consequently, overall, the book is highly authentic, although one inevitably must quibble with the perspectives and points of view of various individuals. This is foreseeable, unavoidable, and healthy.

I found a number of chapters particularly outstanding, including those dealing with cocaine, congenital adrenal hyperplasia, and hemophilia, and with prostate-specific antigen (PSA) as a marker of prostate cancer. Specific points that might be addressed by the authors in the next edition include the following:

The case of lead poisoning (no. 61) emphasizes free erythrocyte protoporphyrin, which is now recognized to be insensitive. Direct measurement of blood lead is the standard. In the chapter on thyroid diseases, in the statement that thyroid stimulating hormone (TSH) is often undetectable in hyperthyroidism, the "often" is misleading. With the very rare exceptions of pituitary resistance to thyroid hormone or pituitary tumor, the TSH should always be undetectable by an acceptable current assay. In addition, the discussion indicates that trophoblastic tumors might not be distinguished with the use of the TSH assay; however, it is to be expected that a specific assay for TSH will not measure human chorionic gonadotropin (HCG) even in the presence of the very high concentrations of HCG associated with trophoblastic tumors. Further, the authors state that it is questionable whether the prevalence of thyroid tumors is increased in Graves disease; this is a misleading alarm. Case no. 33 deals with hypercalcemia and fails to emphasize sufficiently the importance of ionized calcium.

In summary, I am indebted to the authors of this book, who represent a who's who of clinical chemistry for the types of cases presented. I have been in the process of accumulating similar material for teaching purposes. It would be helpful in future editions to be able to separate the comments of the reviewer from those writing the initial discussion.

Let us remember that the product of the laboratory is not isolated data, but rather "medical information." To the extent that the data can be integrated with the case history, the consultant in the clinical laboratory enhances the value of the laboratory to the attending physician and, in turn, to the patient. This book makes a substantial contribution toward empowering clinical chemists in enhancing their contribution.

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