False-Positive Phencyclidine Immunoassay Results Caused by Venlafaxine and *O*-Desmethylvenlafaxine

To the Editor:

We recently observed three occurrences of false-positive results for phencyclidine (PCP) on urine samples tested with the Syva® RapidTest d.a.u.® 9 Test Panel (Syva Company, subsidiary of Dade Behring Inc.). The RapidTest d.a.u. 9 device is a single-use, one-step, solid-phase immunochromatographic assay for the qualitative, discrete detection of several drugs/drug metabolites in human urine *(1)*. The urine samples were collected from three different patients who were seen in our Emergency Department within 3–4 weeks after we had implemented the RapidTest device in our laboratory (Danbury Hospital). Because PCP is not a commonly used drug in our locale and the rare positive results have usually been confirmed as false positives, three positive PCP results in such a short time period immediately aroused suspicion.

Patient A was a 52-year-old male with schizoaffective disorder who was admitted to the psychiatry service. Patient B was a 93-year-old female from a nursing home who was admitted with a hip fracture. Patient C was a 50-year-old female admitted for opiate and benzodiazepine overdose. None of these patients had a history of PCP use or presented with symptoms consistent with use of this drug.

Patient A's urine gave negative results for all other drugs tested with the RapidTest. Patient B's urine also tested positive for benzodiazepines and barbiturates; these results could be attributed to medications documented in this patient's medical record: lorazepam, clonazepam, and phenytoin (the latter is listed in the RapidTest package insert as an interferent in the barbiturates assay). Patient C's urine also tested positive for benzodiazepines and opiates; again, these results were consistent with this patient's known medications (lorazepam and hydrocodone). None of the patients was receiving dextromethorphan, diphenhydramine, ibuprofen, imipramine, meperidine, mesoridazine, or thioridazine—drugs known to produce false-positive results with other PCP immunoassays. The only drug that appeared on the medication lists of all three patients was venlafaxine, a relatively new antidepressant marketed as Effexor® (Wyeth-Ayerst Pharmaceuticals, Inc.) *(2)*. We therefore suspected that this drug and/or one or more of its metabolites were the cause of these false-positive results via cross-reactivity with the anti-PCP antibodies used in the RapidTest devices (cutoff concentration for PCP, 25 μg/L).

Negative results were obtained when the same urine samples from these three patients were tested with the Syva Emit II Plus PCP assay (25 μg/L cutoff) on the Roche Cobas MIRA analyzer (performed at Danbury Hospital). Similarly, analysis by two other single-use immunochromatographic devices, OnTrak TesTstik PCP (Roche Diagnostics) and Biosite Triage 8 DOA (Biosite Diagnostics) also gave negative results for PCP (both 25 μg/L cutoff; performed at Hartford Hospital), and gas chromatographic–mass spectrometric analysis did not detect PCP (5 μg/L limit of detection; performed at Hartford Hospital). Of note, we also encountered a "true-positive" PCP sample from an 18-year-old male patient admitted with head trauma; this urine tested positive for PCP by the RapidTest, Emit, and gas chromatographic–mass spectrometric methods and thus served as a "positive control".

Venlafaxine undergoes both O- and N-demethylation, with the major metabolite, *O*-desmethylvenlafaxine (ODV), also exhibiting antidepressant activity. An average of 87% of a labeled oral dose is excreted in a 48-h urine, with ~5% excreted as parent drug, 29–48% as ODV, 6–19% as di-*N*-desmethylvenlafaxine, and 0.2–7.4% as mono-*N*-desmethylvenlafaxine *(2)*. To further test our hypothesis that venlafaxine and/or its metabolites were responsible for these false-positive results, we obtained pure samples of venlafaxine and the ODV metabolite from Wyeth-Ayerst Research, the manufacturer of this drug. We prepared solutions of venlafaxine and ODV in drug-free urine at final concentrations of 10^6, 10^5, 10^4, 10^3, and 10^2 μg/L venlafaxine or ODV and tested these solutions with both the Emit II and RapidTest PCP assays. The RapidTest gave a clearly positive PCP result (no signal line indicates positive result) at a concentration of 10^6 μg/L of either venlafaxine or ODV and equivocal or borderline results (extremely faint, barely visible line) at 10^5 μg/L of either venlafaxine or ODV, whereas the Emit II assay gave negative results at all concentrations. Additional testing narrowed the concentration where the RapidTest became clearly positive for PCP to somewhere between 1×10^5 and 2×10^5 μg/L of either venlafaxine or ODV, indicating similar cross-reactivities for these two compounds. From these data, we calculated a cross-reactivity of between 0.0125% and 0.025% for both the parent drug and metabolite, using the 50% displacement method described by Miller and Valdes *(3)*. Although at face value this appears to be a very low degree of cross-reactivity, it becomes clinically significant if combined concentrations of venlafaxine and ODV of 1×10^5 μg/L are present in a urine sample.

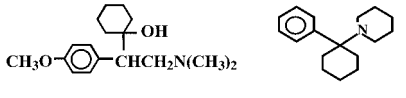
According to the literature, predicted steady-state plasma concentrations of venlafaxine and ODV in healthy individuals receiving daily 150-mg doses are estimated as 70 and 254 μg/L, respectively *(2)*. These concentrations are approximately three orders of magnitude lower than those that were found to give positive results in our addition experiments. Although we could find no published data on urine concentrations of venlafaxine and ODV, we learned that combined concentrations of these two substances on the order of 1×10^5 μg/L have indeed been measured in the urine of patients taking therapeutic doses of venlafaxine (K-T. J. Yeo, personal communication). Combined with the results of our addition experiments, this provides strong evidence that the false-positive results we ob-

served were caused by cross-reactivity of venlafaxine and ODV with the RapidTest PCP assay.

Venlafaxine, designated (*R*/*S*)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol, is a phenethylamine derivative that is chemically unrelated to tricyclic, tetracyclic, and other antidepressants. It is the first antidepressant in a new drug class referred to as the serotonin noradrenergic reuptake inhibitors (SNaRIs) *(4)*. Aside from possessing phenyl and cyclohexyl groups, venlafaxine bears little structural similarity to phencyclidine [1-(1-phenylcyclohexyl)piperidine; see Fig. 1]. Given this structural dissimilarity, it is somewhat surprising that venlafaxine or any of its desmethyl metabolites would cross-react with the anti-PCP antibody used in the RapidTest device. However, other examples of unexpected interferences with immunoassays for drugs of abuse have been well documented in the literature, e.g., oxaprozin with the Emit assay for benzodiazepines *(5)* and efavirenz with the CEDIA test for cannabinoids *(6, 7)*.

In conclusion, we believe our data strongly implicate venlafaxine and ODV as the agents responsible for the false-positive PCP results we observed with the RapidTest device. We have reported our findings to the manufacturer and recommend that all laboratories using these devices be made aware of this cause of false-positive results. Until this interference is eliminated, we have implemented a procedure where all positive PCP results obtained with the Rapid Test must be verified with the Emit II Plus PCP assay before being reported to our Emergency Department.

We gratefully acknowledge the generous contribution of pure samples of venlafaxine and ODV from Wyeth-Ayerst Research, Princeton, NJ.



Venlafaxine Phencyclidine

Fig. 1. Chemical structures of venlafaxine and PCP.

References

1. Peace MR, Tarnai LD, Poklis A. Performance evaluation of four on-site drug-testing devices for detection of drugs of abuse in urine. J Anal Toxicol 2000;24:589–94.
2. Baselt RC, Cravey RH. Disposition of toxic drugs and chemicals in man, 4th ed. Foster City, CA: Chemical Toxicology Institute, 1995:772.
3. Miller J, Valdes R Jr. Methods for calculating cross-reactivity in immunoassays. J Clin Immunoassay 1992;15:97–107.
4. Kent JM. SNaRIs, NaSSAs, and NaRIs: new agents for treatment of depression. Lancet 2000;355:911–8.
5. Camara PD, Audette L, Velletri K, Breitenbecher P, Rosner M, Griffiths WC. False-positive immunoassay results for urine benzodiazepine in patients receiving oxaprozin (Daypro™). Clin Chem 1995;41:115–6.
6. Physicians' desk reference, 55th ed. Montvale, NJ: Medical Economics Company, 2001:1158.
7. Sustiva yields false positives on marijuana tests. Crit Path AIDS Proj 1998;Fall(No 33):65.

Salvador F. Sena[1]*
Syed Kazimi[1]
Alan H.B. Wu[2]

[1] *Department of Pathology and Laboratory Medicine Danbury Hospital Danbury, CT 06810*

[2] *Department of Pathology and Laboratory Medicine Hartford Hospital Hartford, CT 06102*

*Author for correspondence. Fax 203-731-8678; e-mail salvador.sena@danhosp.org.

False-Positive Troponin I Attributed to a Macrocomplex

To the Editor:

Cardiac troponins (I and T) represent a major improvement in the biochemical approach to the detection and evaluation of myocardial damage *(1, 2)*. Here, we describe a case in which the measurement of cardiac troponin I (cTnI) gave erroneous clinical information because of interference caused by the presence of a macrocomplex.

The patient, a 78-year-old Caucasian woman with a pacemaker, had a long-standing history of cardiac disease, including a myocardial infarction 1 year before (July 1999), transient ischemic episodes with chest pain, and mitral valve failure. On July 22, 2000, the patient was admitted to the cardiac intensive care unit for an episode of chest pain and dyspnea. On admission, no significant electrocardiographic alterations were found. Biochemical markers were measured on several occasions (e.g., Table 1). Reference values were according to the manufacturers and confirmed in our population. At admission, cTnI and myoglobin (RxL Dimension; Dade-Behring) were increased (1.0 and 96 μg/L, respectively; reference values $<$0.05 and $<$70 μg/L), but creatine kinase MB (CK-MB) was not (2 μg/L; reference value $<$5 μg/L). The patient was moved from the intensive care unit to a medical department on the 2nd day after admission. cTnI ranged from 0.9 to 1.1 μg/L, myoglobin gradually decreased to within the reference interval, and CK-MB remained within normal limits, ranging from 1.5 to 2.3 μg/L. After July 29 (7th day of admission), a progressive increase was observed in cTnI, with the maximum of 10.2 μg/L observed on August 17 (the 26th day after admission).

The patient was discharged as the increased cTnI values were not associated with a worsening clinical status. At follow-up, cTnI values were persistently increased (17.4, 19.0, and 18.8 μg/L on the 34th, 39th, and 47th day after initial presentation, respectively), whereas CK-MB and myoglobin were within their reference intervals. On the 74th day after initial presentation (October 4, 2000), cTnI was still increased (4.0 μg/L) but had decreased from the September 7 value. The variations observed were not ascribable to the imprecision of the assay because the CV was $<$3% at those concentrations. We found no alterations in renal function or in electrocardiographic or clinical findings in relation to the increased cTnI.

The constant increases in cTnI were also confirmed with the Triage System (Biosite Diagnostic; cTnI values, 23.0, 22.8, and 15.6 μg/L; refer-