mophore undergoes a bathochromic shift in the presence of an aprotic solvent and a base to give a blue derivative with maximum absorbance at 600 nm. Hitherto, we observed neither positive nor negative interferences.

Recently, however, we observed the development of a pink color in the final stage of the procedure, masking the blue color of VMA (Fig. 1). The urine sample in question came from a pediatric patient with neuroblastoma, who was receiving etoposide and carboplatin chemotherapy.

Etoposide is a complex organic molecule with a dimethoxyphenol residue attached to the central naphthalene ring in a trans-configuration [2]. To test the possibility of a diazo reaction with etoposide, we added increasing amounts of etoposide to a control urine and measured the apparent VMA. No increase in VMA concentration was observed over a range of etoposide concentrations from 10 to 500 mg/L of urine. This nonreactivity could be either mechanistic or related to nonextractability of the etoposide. By processing etoposide through our procedure and then measuring the absorbance at 296 nm, we found that <0.1% of the etoposide reached the final measuring step. Furthermore, reaction of etoposide with the diazo derivative added in the final step produced a yellow color rather than the pink seen in the patient’s sample (Fig. 1).

Etoposide undergoes extensive hepatic metabolism and excretion by the kidneys [3]. Allen et al. [4] isolated the major urinary metabolite of etoposide and identified it by mass spectrophotometry as 4-demethylpodophyllinic acid. The features of this compound make it a good candidate for reaction with a diazo derivative: an aromatic phenolic residue as possible site for reaction and a carbonyl group to carry the molecule through the extraction steps of our procedure. Other metabolites excreted in smaller amounts, i.e., picroetoposide and the aglycone, are for purely structural reasons not expected to react positively in the assay. The patient’s urine gave a normal VMA spectrum 10 days after therapy with etoposide was stopped.

Several metabolites as well as xenobiotics interfere with many diazo methods used in the determination of VMA [5]. The reaction of a diazo derivative with carboplatin is highly unlikely, this simple organo-metallic compound being devoid of activated aromatic residue. Further work is under way to isolate and test the major metabolite.

We recommend that VMA analysis by use of any diazo derivative such as ours or some other [6] be interpreted with caution in patients receiving etoposide. Alternatively, methods with high resolving powers such as thin-layer chromatography [7] or HPLC [8] should be considered.

References

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Serum Cardiac Troponin I, Creatine Kinase (CK), and CK-MB in Early Posttraumatic Rhabdomyolysis

To the Editor:

Early diagnosis of posttraumatic cardiac injury is important for patient outcome [1] but a concomitant rhabdomyolysis may impede its detection by biochemical means. Cardiac troponin I (cTnI) might be a useful tool to specifically assess myocardial damage in trauma patients. We re-
port here serum cTnI, creatine kinase (CK), and CK isoenzyme MB measurements in multiple injured patients with rhabdomyolysis.

Successive trauma patients with rhabdomyolysis [CK activity >500 U/L] during the first 24 h after admission were studied in accordance with the Helsinki Declaration. Exclusion criteria were age >55 years, Injury Severity Score (ISS [2]) <16, and history of prior cardiac or renal disease. Patients were considered to have chest trauma when the chest Abbreviated Injury Score [3] was ≥2.

Electrocardiography and a transesophageal echocardiography (HP Sonos 1000 with a biplane 5.5 MHz transducer; Hewlett-Packard, Courtaboeuf, France) were performed as soon as possible within 48 h after admission and repeated if needed. Blood was sampled 12 and 24 h after admission. Total CK activity was assessed according to IFCC recommendations but at 37 °C. CK-MB mass and cTnI were measured in duplicate (the second analysis after a freeze-thaw cycle and repeat centrifugation) with commercially available immunoassays (Stratus CK-MB and Stratus cTnI; Baxter Dade, Maurepas, France); reference values were <7 μg/L and <1.6 μg/L, respectively. The CK-MB mass index was calculated as follows: 100 CK-MB (μg/L)/total CK (U/L); our in-house reference upper limit was 1.1. Results are given as median (and range of all data).

We studied 18 patients [age 30 (20–48) years; ISS 31 (16–61)]; 9 had a chest trauma but no segmental wall motion abnormality or Q wave or ischemic changes. Peak total CK activity was 3448 (540–13 170) U/L. As shown in Fig. 1, peak CK-MB was above the discrimination value for myocardial infarction in 13 patients (6 chest traumas), CK-MB mass index was abnormal in 4 patients (3 chest traumas), and peak cTnI was above the reference limit in 6 patients (5 chest traumas). The correlation between peak CK-MB and peak total CK was strong (r = 0.81, P = 0.0009), but we saw no relation between cTnI and total CK or CK-MB.

Thus, as previously described in nontraumatic rhabdomyolysis [4], the significant relation between total CK and its isoenzyme indicates that CK-MB is not a valuable indicator of myocardial injury in the trauma setting. Likewise, increasing specificity by using the CK-MB index was obtained at the expense of sensitivity [5].

cTnI is proposed as a highly sensitive marker of cardiac damage [6], and the absence of this structural protein in fetal and adult skeletal muscle confirms its cardiac specificity [7]. Significant cTnI serum concentrations without clear evidence of myocardial injury in medical patients [4] or trauma patients (present report) may signify that the clinical component of the diagnosis is incomplete or less sensitive than the biological one, leading to an overestimation of the incidence of “false-positive” results [5]. This high sensitivity was recently illustrated by an increased cTnI concentration in a patient with an isolated posttraumatic pericardial effusion probably related to a limited cardiac contusion despite normal echography [5].

We conclude that cTnI remains a valuable tool for the detection of subclinical myocardial damage in patients with skeletal muscle injury, especially in the presence of chest trauma. Indeed, it is probably more sensitive than the available clinical means. A significant increase in cTnI after trauma therefore justifies reinforced early cardiovascular monitoring and prolonged follow-up care.

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References


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