False-Positive Plasma Troponin I with the AxSYM Analyzer

To the Editor:
The AxSYM System Analyzer (Abbott Laboratories, Abbott Park, IL) is frequently utilized in the measurement of cardiac enzymes, hormones, drugs, and other markers. Falsey increased troponin I (TnI) results attributable to the presence of heterophilic antibodies (1), rheumatoid factor (2), or fibrin clots (3) have been described previously. We report several cases of erroneously increased results for plasma TnI that were attributable to a temporary malfunction of the AxSYM analyzer. The impairment of the analyzer was noted during one of the daily control runs when the three plasma TnI and creatine kinase-MB (CK-MB) quality-control samples repeatedly exceeded their respective control ranges. The instrument did not display an error code for a mechanical or other problem. In an effort to ascertain the cause of the spurious quality-control result, we opened the instrument cover to inspect the processing center. We checked the positions of two bulk solution dispensers (located within the AxSYM processing center). The dispensers, labeled “1” and “3”, were side-by-side, adjacent to the microparticle enzyme immunoassay (MEIA) optical assembly, processing center pipette, and processing carousel. Upon more detailed inspection, we found that bulk solution dispenser 3 was misaligned: its nozzle, to direct wash solution 3 to the matrix cell, was in an off-center position. After realignment, we repeated the TnI and CK-MB quality-control analysis; this time the results were within their respective control ranges.

We next reviewed results reported before the erroneous quality-control results. Twenty-nine TnI measurements had been reported since the previous, accepted quality-control runs. (No CK-MB measurements had been reported within the interval.) Comparison of reported results with the reference range had yielded 8 positive (11.6 ± 6.9 μg/L, mean ± SD), 4 intermediate (1.2 ± 0.4 μg/L), and 17 negative (<0.5 μg/L) results. All 29 samples were re-analyzed after dispenser 3 was realigned. One result remained positive, 1 result was intermediate, and the remaining 27 were negative.

Hypothesizing that misalignment of dispenser 3 was the source of the discrepant TnI and CK-MB quality-control results and the cause of the falsely increased TnI reported results, we purposely misaligned dispenser 3 and performed quality-control measurements for TnI, CK-MB, vancomycin, acetaminophen, and salicylate. Again, error codes were not displayed by the analyzer. Validating our hypothesis, the TnI and CK-MB results exceeded their respective control ranges, whereas vancomycin, acetaminophen, and salicylate quality-control measurements were within their corresponding ranges.

We selected four patient samples and analyzed them while dispenser 3 was correctly aligned. We then repeated the troponin measurement after purposely misaligning dispenser 3. After misalignment, two TnI results were elevated by an order of magnitude compared with their previously low positive values (from 3.8 ± 0.6 to 48.3 ± 1.2 μg/L, and two TnI results became positive compared with previously negative values (from <0.5 to 16.0 ± 1.6 μg/L). Subsequently, all experiments described above were repeated with dispenser 3 properly aligned and dispenser 1 purposely misaligned. TnI and CK-MB analysis led to the display of an error code: “INVALID TEST RESULT. INTERCEPT TOO LOW”. Vancomycin, acetaminophen, and salicylate quality-control measurements were within their respective reference ranges.

Our data indicate that misalignment of bulk solution dispenser 3 produced falsely increased TnI and CK-MB measurements without display of an error code by the instrument. Because both TnI and CK-MB results contribute to the diagnosis of acute myocardial infarction, falsely increased results for these cardiac markers confer a considerable risk of morbidity and mortality, especially in the event of an invasive therapeutic procedure. In addition to the guidelines provided by the manufacturer, we recommend checking the alignment of bulk solution dispenser 3 after every occasion in which the cover to the instrument’s processing center is opened.

In summary, our data indicate that misalignment of bulk solution dispenser 3 produced falsely increased TnI and CK-MB measurements without display of an error code by the instrument. Because both TnI and CK-MB results contribute to the diagnosis of acute myocardial infarction, falsely increased results for these cardiac markers confer a considerable risk of morbidity and mortality, especially in the event of an invasive therapeutic procedure. In addition to the guidelines provided by the manufacturer, we recommend checking the alignment of bulk solution dispenser 3 after every occasion in which the cover to the instrument’s processing center is opened.

References
To the Editor:

We read with interest the case conference by Fantz et al. (1) on thyroid function during pregnancy. The presented case is typical of gestational thyrotoxicosis (2), and the authors reviewed beautifully the related problems of interpretation of thyroid function tests in pregnancy.

We had proposed a new clinical entity, “gestational thyrotoxicosis”, defined by clinical features as follows (3): (a) thyrotoxic symptoms, such as palpitation, increased sweating, and weight loss in early pregnancy; (b) marked increase in free thyroxine (T4; more than twice the upper limit of the reference range) and free triiodothyronine (T3); (c) complication with hyperemesis gravidum; (d) spontaneous recovery in the later half of pregnancy; (e) negative for antithyroid microsomal or thyroid peroxidase antibodies; (f) negative for anti-thyroid-stimulating hormone (TSH) receptor antibodies; (g) no goiter; and (h) circulating human chorionic gondadotropin (hCG) with high biological activity.

We examined the case of Fantz et al. (1) in light of our experience. They did not examine the anti-thyroid antibodies in their case, although the importance of antibody measurement was described in the discussion.

Their laboratory data on thyroid function are curious. The free T4 index was more than fourfold higher than the upper reference value of nonpregnant healthy subjects, but the TSH was 0.8 mIU/L (1). The negative feedback regulation in the pituitary-thyroid axis was well preserved even during pregnancy (4); thus, TSH should completely be suppressed. The TSH value of 0.8 mIU/L might be obtained if high hCG α-submit interfered in the assay or if the sample was obtained at a different date than the free T4 sample.

The increase of serum thyroglobulin concentration in normal pregnancy may not be correct. Earlier reports on thyroid function tests in pregnancy from European countries mainly observed the effect of relative iodine deficiency rather than physiological gestational changes because iodine intake is relatively low in these countries and iodine requirements are increased during pregnancy. Iodine supplementation during pregnancy decreases, rather than increases, thyroglobulin (5). Decreased serum thyroglobulin in pregnancy is compatible with a previous report from Japan where iodine intake is sufficient (6). A recent study in the United States also clarified that there was no significant change in thyroglobulin concentration during and after normal pregnancy (7). Gestational thyrotoxicosis is induced mainly by the overstimulation of asialo-hCG, which has strong thyroid stimulation bioactivity (2). The conventional immunoassay for hCG cannot specifically detect asialo-hCG, and thus, the serum concentrations of hCG in gestational thyrotoxicosis did not differ significantly from those in euthyroid normal pregnant subjects (2).

In the cases of Graves thyrotoxicosis, measurement of anti-TSH receptor antibodies (TRAbs) is important for diagnosis, as the authors discussed. The radioreceptor assay for TRAbs was developed first by Smith et al. (8) in the United Kingdom, and they used the term “TSI”. Therefore, TSI indicates TRAbs measured by radioreceptor assay and does not express biological activity. At present, the term TSH receptor-binding inhibitory immunoglobulin (TBI) is widely used (9). Instead of TSI, thyroid-stimulating antibody (TSAb) is commonly used for the expression of biological stimulating activity. Thyroid growth-stimulating immunoglobulin (TGI) is somewhat difficult to assay for a routine test, and there is still debate whether TGI is the same as TSAb.

Fantz et al. (1) are thoughtful to discuss postpartum thyroid dysfunction because this problem is far more common than gestational thyrotoxicosis. Our recent review provides further discussion of the clinical importance of postpartum thyroid dysfunction (10).

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References


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The manager of AxSYM System Integration for Abbott Diagnostic Division responds:

To the Editor:

In their letter, Galambos et al. indicate the importance of following good laboratory practice with any procedure. In the AxSYM System Operation Manual, Revision 3, Volume 1, Section 8, page 19, we caution users stating, “Correct installation of the Bulk Solution Dispensers is required for the proper dispensing of solutions. Assay results can be adversely affected by improper dispensing of Solutions 1 and 3”. In general, when operator intervention is required, every effort should be made to ensure proper setting of instrument components.

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Clinical Chemistry 46, No. 7, 2000

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