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Validity of a Point of Care Device (Cholestech LDX) to Monitor Liver Enzyme Activity (Aminotransferase Measures) During a Clinical Trial

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Abstract

Background—Serum transaminase activity is a common measure of liver injury used in clinical trials. The use of a point-of-care device to monitor serum transaminases would allow immediate evaluation of this safety endpoint and may be less expensive than standard laboratory testing.

Purpose—The objective of this study was to compare a point of care transaminase test to a standard laboratory measurement.

Methods—Subjects were healthy adults participating in a clinical trial measuring the effects of therapeutic doses of acetaminophen on serum transaminase activity. For this study, serum transaminase activity was determined every 3 days for 14 days. At each measurement, a sample was sent to the clinical laboratory for measurement and also analyzed using a point of care device (Cholestech LDX, Hayward CA). The results were compared using a Bland-Alman plot to identify bias and we also measured the agreement between the techniques for categorizing samples as “low”, “normal” or “elevated”.

Results—One hundred thirty three samples from 35 subjects were compared. The 95% confidence interval for the limits of agreement between the LDX and the clinical laboratory was –8.46 to 27.09 IU/L. Agreement for classification as low, normal or elevated was moderate between the two methods (Kappa=0.37).

Conclusion—The point of care device provided moderate agreement with the laboratory transaminase measurement. However, use of the device would have resulted in misclassification of approximately 1/3 of samples. We do not recommend this point of care device for the measurement of serum transaminases in clinical trials.

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Background

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are enzymes that are primarily produced in hepatocytes and released into the systemic circulation with hepatocyte death. The serum activity of these enzymes is a measure of hepatic injury, and they are used for disease diagnosis management and can detect liver injury from medications.

Monitoring of aminotransferase levels is common in clinical trials involving pharmaceuticals to evaluate the risk for drug induced liver injury associated with the investigational drug. Recently, a draft guidance for drug-induced liver injury was released which lists specific stopping criteria when investigating new drugs. This criterion relies on ALT and AST measures; If these measures become abnormal the patient will require additional testing such as the International Normalized Ratio (INR) and bilirubin to make the diagnosis of drug-induced liver injury.[1] Therefore real-time determination of the AST and ALT is an important safety measure in clinical trials evaluating medications.

Point of care testing (POC) is the performance of laboratory testing in the patient care setting rather than in a remote laboratory. POC testing has been shown to shorten patient stay and provide clinically relevant information to healthcare providers faster than standard laboratory testing.[2;3]. The Cholestech LDX (LDX) is a point of care machine able to determine aminotransferase levels as well as a lipid panel depending upon the cartridge used. These levels can be obtained using whole blood or serum, and results are available within 5 minutes. While no specific sample collection method is specified in the product insert, collection of whole blood via fingerstick is recommended and the supplies required for fingerstick blood collection are sold directly from the LDX manufacturer. If this device provides accurate measurement of the ALT and AST, the ease of use and low cost would make it appealing for use in clinical trials.

The objective of this study is to describe the use of the LDX for monitoring ALT and AST during a clinical trial and to validate the use of LDX by comparing results to those obtained from a clinical laboratory.

Methods

The validation of the LDX was done during an open-label prospective drug safety trial of 35 healthy volunteers from August 31, 2007 through January 14, 2008. Six serial samples were collected for each participant (study days 0, 4, 7, 9, 11 and 14). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) measures were obtained from both the institution's Clinical Laboratory Improvement Amendments (CLIA) certified clinical laboratory and the LDX rapid result machine. At each study visit, blood was collected in a serum separator vacutainer tube using a butterfly collection kit to send for aminotransferase testing at the clinical laboratory. Immediately following the conclusion of the draw, the remaining blood in the butterfly tubing was used to determine aminotransferase levels from the LDX machine. Results from both sources were required to be included in this analysis.

The LDX machine was calibrated and controls were run according to the product insert.[4] Study personnel collecting the samples were trained on site by the LDX manufacturer. All processes of control testing, calibration, active cassettes used and results were documented. The normal range listed in the LDX product insert was 10–40 IU/L for ALT and 10–30 IU/L for AST with a coefficient of variation of 4.2% for ALT and 4.8% for AST. The measuring range for ALT and AST was 10 to 400 IU/L. Results outside this range are reported as <10 U/L or >400 U/L.[4]

The clinical laboratory used for this study was located at a 500 bed urban safety net hospital. At the time of the study, the laboratory used the Roche-Hitachi Modular Analyzer to perform aminotransferase assays. The normal range for ALT at this laboratory was 5–40 IU/L for men and 5–36 IU/L for women. The normal range for the AST was 9–36 IU/L for both men and women.

Our primary comparison was the difference between the laboratory and the LDX ALT values for each paired sample. The difference was defined as (laboratory values minus LDX value). We then calculated the mean and variance for the differences of ALT and AST. In addition, we used a Bland-Altman plot to describe any bias in the measurements over the range of sample values. Separate analyses were conducted for ALT and AST. For all pairs of measurements ($n=135$), the mean of the two values of comparison were plotted against the difference of the two values. The mean difference summarizes the overall difference occurring within pairs, and the 95% agreement limits (± 2 standard deviations) help display variance of differences. Since ALT and AST results were obtained from multiple samples within the same individuals, the variance for the paired differences was calculated using methods to accommodate repeated measures.[5–7] R, version 2.5.1, was used to create Bland-Altman plots.

As a secondary analysis we measured ALT agreement between the two methods by categorizing the samples as low (Lab: <5 , LDX: <10), normal (Lab: 5–36 female, 5–40 male, LDX: 10–40) or high (Lab: >36 female, >40 male, LDX: above 40) based on the normal range established by the laboratory and by the range suggested by the LDX package. We used a kappa statistic with 95% confidence intervals to measure agreement between the methods.

Results

A total of 35 subjects were enrolled in the study. Results from both the LDX and laboratory were obtained for 133 samples from 28 subjects for ALT and 136 samples and 29 subjects for AST. Samples with results from only one method were excluded from this analysis. Overall we were able to measure ALT successfully in 66.2% of attempts and AST in 67.7% of attempts as the LDX device required service during a portion of the study.

Of the 29 subjects that had at least one paired sample of ALT or AST, 9 (31%) were male. The mean age was 37.5 (32.9, 42.0) years and the primary ethnic origin was Caucasian (87%). The overall mean ALT obtained from the clinical laboratory and the LDX was 37.8 IU/L and 28.5 IU/L, respectively. The laboratory mean value was 9.3 (7.8 to 10.8) IU/L higher than the values obtained with LDX. The overall mean AST obtained from the clinical laboratory and the LDX were 30.8 and 27.1 IU/L respectively. The overall mean laboratory value was 3.7 IU/L (2.7 to 4.8 IU/L) higher than the value obtained with LDX.

A scatterplot of the clinical laboratory ALT values and the LDX ALT values is shown in Figure 1. If the values were in perfect agreement, the values would fall on the line of agreement. This figure shows that the laboratory values are generally higher than the LDX values. The Bland-Altman results indicate that the ALT values obtained from the LDX were on average lower than those reported by the clinical laboratory (Figure 2). The mean difference between the clinical lab and LDX ALT results was 9.32, and the 95 percent agreement limits were -8.46 to 27.09 . This means that 95 percent of observed LDX values are expected to be within 8.46 IU/L lower to 27.09 IU/L higher than paired laboratory values. The range defined by the agreement limits spans 35.5 IU/L; this is wide considering the normal lab value of ALT is less than or equal 40 IU/L. The Bland-Altman plot of AST (Figure 3) also indicates that clinical lab values are higher than LDX; the mean difference was 3.74 (95% agreement limits: -8.68 , 16.17). AST also has a wide interval (24.9 IU/L) of expected differences. Overall, both plots

show greater differences corresponding to higher mean values. This suggests that disagreement between the clinical and LDX values increase as the mean ALT and AST values increase.

When the ALT samples were categorized into low, normal and high values, no samples were categorized as low by either method. The LDX categorized 114 samples as normal and 19 samples as high, while the laboratory categorized 77 as normal and 56 as high. The Kappa statistic showed marginal agreement (Kappa=0.37, CI 0.24 to 0.51), however the interpretation of Kappa's significance should be interpreted cautiously since the repeated measures data do not meet the assumption of independent observations.

The unit cost for each sample on the LDX device was approximately \$5 per cassette and the cost for the device was approximately \$2000. The handling, preparation and staff training time were minimal. Our clinical laboratory charged 60 dollars each for ALT and AST measurement, and the samples had to be transported to the clinical laboratory. As transaminase monitoring was a safety requirement, we could not bank and run "batch samples" to receive a research discount price. This suggests that exclusive use of the LDX would produce significant cost savings.

Discussion

The LDX device provided rapid, inexpensive transaminase results using a small blood sample. However, we found that the results from the LDX were systematically lower than those measured in the clinical laboratory by 9.3 and 3.7 units, and that the LDX results were more likely to underestimate higher ALT and AST measurements. Furthermore, agreement between the laboratory determinations and the LDX was modest. Two-thirds of the samples categorized as high by the laboratory were categorized as normal by the LDX. This would mean that LDX-determined results would underestimate the proportion of subjects with abnormal ALT. This observation is similar to the discrepancies that have been described when results are compared between clinical laboratories.[8] Overall, the performance of the LDX when compared to our laboratory suggests that the LDX should not be used for close measurement of the ALT in a clinical trial.

There are several theoretical advantages to using a point of care device to monitor transaminases during a clinical trial. The immediate results allow rapid decisions about subject continuation. For example, our study required that subjects have normal ALT at baseline. Point of care transaminase determination allowed us to exclude patients during the screening exam without venipuncture and without requiring the investigator to wait until the laboratory results were posted to inform the study subjects. Point of care testing also offers the potential for real-time identification of subjects who reach protocol stopping points during study visits. Rapid identification would allow subjects to be removed from treatment immediately and avoids the need for delayed contact once the clinical laboratory results are available. This would prevent the excess risk that might occur if the researcher were unable to contact the subject and the subject continued using the study medication. For the purposes of our study we could not confidently rely on the LDX readings to closely monitor transaminase activity as the agreement between the LDX and our reference laboratory was so poor. Additionally, the high rate of misclassification negated the advantage of rapid result.

Limitations

There are limitations to our findings. First, the blood samples used were not collected by fingerstick as recommended by the manufacturer. However, there is no reason to believe that this would systematically alter the results from the LDX. Second, the LDX measured ALT and AST in whole blood while the reference laboratory used sera. While this might alter the absolute values, the LDX has been shown to be highly correlated with the serum measurement.[4]

Furthermore, we defined abnormal values using the range reported in the product insert. This should account for systematic differences in measurement when categorizing values as normal or abnormal. Finally, while we studied subjects with a wide range of ALT and AST values, our sample did not include subjects with marked ALT elevations or any samples with measurements below the normal range. The maximum quantitative level of the LDX is 400 U/L for both ALT and AST. The LDX product insert states that enzyme activity greater than 1000 U/L could yield falsely low results and cautions against using the device in this instance.[4] As low ALT and AST measurements are not of clinical or research interest, we feel that the lack of low samples has little implication for our findings.

The highest ALT value recorded was 159 IU/L from LDX and 136 IU/L from the laboratory and the highest AST value noted was 78 IU/L from LDX and 100 IU/L from the laboratory. Validity of higher values, particularly those >500 IU/L are unknown. As mentioned in Green 2008 [8], more disparate results were seen between clinical laboratories with higher ALT measures, same appears to be true when comparing LDX to laboratory with limited samples.

Conclusions

Although the Cholestech LDX was easy to use and inexpensive, the device systematically underestimated the serum ALT and AST. When used in a clinical trial, this underestimation could produce misclassification in a substantial number of subjects. While the accuracy of the LDX may be acceptable for clinical use, we do not believe the LDX is acceptable for close monitoring of serum transaminase activity in a clinical trial. It may be useful for basic screening or safety monitoring if some deviation from the laboratory measured values are acceptable.

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Reference List

1. Drug-Induced Liver Injury: Premarketing Clinical Evaluation: United States Food and Drug Administration. 2007 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072278.pdf>.
2. Loten C, Attia J, Hullick C, Marley J, McElduff P. Point of care troponin decreases time in the emergency department for patients with possible acute coronary syndrome: a randomised controlled trial. *Emerg Med J* 2010;27:194–198. [PubMed: 20304883]
3. Leal S, Soto-Rowen M. Usefulness of point-of-care testing in the treatment of diabetes in an underserved population. *J Diabetes Sci Technol* 2009;3:672–676. [PubMed: 20144311]
4. Cholestech LDX ALT AST Product Insert: Cholestech. 2004 at <http://www.cholesteck.com/docs/ldx/ALT-AST.pdf>.
5. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999;8:135–160. [PubMed: 10501650]
6. Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. *J Biopharm Stat* 2007;17:571–582. [PubMed: 17613642]
7. [R] Bland-Altman method to measure agreement with repeated measures. The R-Help Archives.: Nutter, B. 2008 at <https://stat.ethz.ch/pipermail/r-help/2008-July/166921.html>.

8. Green JL, Campagna E, Bogdan GM, Dart RC, Heard K. Effects of clinical laboratory choice on study outcome: an interlaboratory evaluation of aminotransferase levels. *Pharmacotherapy* 2008;28:453–457. [PubMed: 18363529]

Figure 1.

Scatterplot of ALT values determined by the clinical laboratory and LDX device. The dashed line shows the line of perfect agreement and the solid line shows the line of best fit for the observed data.

Figure 2.
Bland-Altman plot comparing ALT results from LDX and Clinical Laboratory. Shaded area shows the normal range for averaged values.

Figure 3.
Bland-Altman plot comparing AST results from LDX and Clinical Laboratory. Shaded area shows the normal range for averaged values.