Available online at www.medicinescience.org

ORIGINAL RESEARCH

Medicine Science International Medical Journal

Medicine Science 2018;7(3):544-7

Measurement uncertainty in biochemical parameters

Selda Telo, Dilara Kaman

Firat University Faculty of Medicine, Department of Biochemistry and Clinical Biochemistry, Elazig, Turkey

Received 23 January 2018; Accepted 09 March 2018
Available online 18.04.2018 with doi: 10.5455/medscience.2018.07.8769

Abstract

Measurement uncertainty is a quality indicator that is used to show the distribution level of a test result in a laboratory. The aim of this study is to calculate the measurement uncertainty of ten biochemical parameters investigated in our laboratory and compare the obtained values with the permissible total error values (% TEa), which various authorities determine for these tests. The measurement uncertainty of glucose, ALT, AST, urea, creatinine, sodium, potassium, albumin, total protein and total cholesterol were investigated in the biochemical auto analyzer (Siemens Advia 2400). Fifty randomly selected 2 level (low and high) internal quality assessment results and external quality assessment of six-month data, the first six months of 2016, were calculated for each test. Nordtest guide was used for the measurement uncertainty calculation. The measurement uncertainties were calculated as 3.9%, 6.72%, 3.4%, 8.06%, 9.06%, 6.08%, 5.02%, 4.98%, 4.96% and 7.22% for glucose, ALT, AST, urea, creatinine, albumin, total protein and total cholesterol, respectively. The calculated measurement uncertainties were found to be lower than the CLIA'88 and RiLi-BEAK % TEa values, except for sodium. Calculated % TEa values for creatinine, sodium, total protein and albumin were found to be higher than Fraser % TEa values. A test result or a measurement is not sufficiently effective when reliability is not assessed. Laboratories should calculate the measurement uncertainty for each parameter. They should give the results that do not exceed the targeted % TEa values. Clinicians should be informed about the measurement uncertainties so that they consider it while evaluating patient results.

Keywords: Measurement uncertainty, biochemical tests, quality control

Introduction

Uncertainty is an interval that contains the values given together with a result of a measurement or a result of a test and the values with the possibility to be attributed to the measurement magnitude [1]. The paradigm of measurement uncertainty, which emerged during the early 20th century, claims that uncertainty is not a drawback but a property of the result of the measurement [2]. The term measurement uncertainty covers the information about the real value of the result and the factors that influence the result. In order to estimate the uncertainty of a measurement, random and systematic errors should be clarified and the effect of each major component on the measurement uncertainty should be determined by suitable methods [3]. Measurement uncertainty is a quantitative indicator of an obtained result. In other words, it demonstrates the extent to which the result represents the real value [4]. Measurement uncertainty is significant for the evaluation of method's availability for clinical implementations and for the comparison of similar types of results. An extensive evaluation of the components that contributes to the measurement uncertainty also reveals the points to which attention should be paid in order to verify the measurement procedure of a test method [5]. When the measurement of uncertainty is presented together with the result, it provides an information regarding the quality of the measurement to the users of the result [4]. Calculation of the measurement uncertainty and its presentation along with the measurement demonstrates the borders within which the measurement is placed, and the level of reliability and quality of the measurement. Thus, measurement uncertainty is required while making medical decisions, comparing measurement results, deciding the conformity within limits[6]. A number of factors, such as matrix effect, interferences, reference materials, mass and volume uncertainties, environmental factors, method and procedure of the measurement and the operative, contribute to the measurement uncertainty [1,5-7].

Clinical Laboratory Implementation Amendments' 1988 (CLIA '88) criteria specify the maximum limit of error that is allowed legally for the measured material in European countries [8]. Just as CLIA, RiLi-BAEK criteria in Germany are available for the total error measurements [9]. The aim of this study is to calculate the measurement uncertainty values for each of the ten-biochemical parameters, which are used in our laboratory, by making use of the internal and external quality control data and compare these calculated values with the total error allowed percentage (%TEa) values of CLIA, RiLi-BAEK and Fraser.

***Coresponding Author:** Selda Telo , Firat University Faculty of Medicine, Department of Biochemistry and Clinical Biochemistry, Elazig, Turkey
E-mail: drseldatelo@hotmail.com

Material and Method

TIn this study, the measurement uncertainty calculation model that was defined in the Nordtest guideline was adopted [10]. All of the biochemical analytes were studies by using the Siemens Advia 2400 auto analyzer and by using the kits belonging to the same firm. For each parameter, the percentage value of total allowed error from CLIA, RiLi-BAEK and Fraser was determined.

1st Step: In order to calculate the reproducibility within-laboratory (Rw), the %CV (variation coefficient) values for 1st and 2nd level control materials were used (Table 1).

%CV = (the standard deviation of the measurement/mean of measurement)x100.

$$Rw = \sqrt{(1^{st}\ \text{level control \%CV})^2 + (2^{nd}\ \text{level control \%CV})^2}$$

uRw=Rw/2

2nd Step: RMS bias and u(Cref) values are used for the calculation of the uncertainty from the external quality control data [u(bias)] component. Bias is expressed as the difference between the real and the measurement value [8]. The data that was obtained by the KBUDEK programme was used in the bias calculation. For this calculation, intragroup and intergroup bias values were calculated (Table 2).

$$\text{RMS bias} = \sqrt{[(\text{intragroup bias})^2 + (\text{intergroup bias})^2]/2}$$

Intragroup bias2=Σintragroup bias2/n
Intergroup bias2=Σintergroup bias2/n
n=the number of external quality control contribution

u(Creft) is the coefficient of variability (CV) of the laboratory results that are included in the external quality control program and placed in the same group. The %CV value was used in the calculation of the u(Cref) external quality control value (Table 2).

$$u(Cref) = \%CV / \sqrt{n_{Lab}}$$

n=the number of laboratories that use the same method and the same device

3rd Step: All of the uncertainty values were converted into the standard uncertainty [u(bias)] value (Table 2).

$$u(bias) = \sqrt{\text{RMS bias}^2 + u(Cref)^2}$$

4th Step: By making use of all of the standard uncertainty components, a combined standard uncertainty (UC) value was calculated (Table 2).

$$Uc = \sqrt{(uRw)^2 + [u(bias)]^2}$$

5th Step: The value of combined standard uncertainty was multiplied by the k factor in order to calculate an expanded uncertainty value. K value was regarded as approximately 2, which represents 95% reliability as 1.96 (Table 2).

U=2.uc

6th Step: The expanded uncertainty value (U) was evaluated by using the allowed total error limits (%TEa) by Westgard (Table 3).

Results

The measurement uncertainties were determined to be 3.9%, 6.72%, 3.48%, 8.06%, 9.06%, 6.08%, 5.02%, 4.98%, 4.96% and 7.22% for glucose, ALT, AST, urea, creatinine, sodium, potassium, albumin, total protein and total cholesterol, respectively. It was determined that the measured uncertainties were lower than the CLIA '88 's and RiLi-BAEK's %TEa values, except for sodium. It was also determined that the measured %TEa values for creatinine, sodium, total protein and albumin were higher than the %TEa values of Fraser (Table 3).

Table 1. Internal quality control % CV values and uncertainty's uRw values

Analytes	Low control material % CV	High control material % CV	uRw
Glucose	1.82	2.49	1.54
ALT	3.74	4.71	3.01
AST	2.48	2.21	1.66
Urea	1.96	1.78	1.32
Creatinine	3.72	1.71	2.04
Sodium	1.98	1.6	1.27
Potassium	2.57	1.58	1.50
Albumin	1.73	1.73	1.22
Total protein	2.85	2.64	1.94

Table 2. External quality control RMSbias, u(Cref) values and standard, combined and expanded uncertainty values

Analytes	RMSbias	u(Cref)	u(bias)	uc	U(%)
Glucose	1.21	0.1	1.21	1.95	3.9
ALT	1.51	0.23	1.52	3.36	6.72
AST	0.48	0.26	0.53	1.74	3.48
Urea	3.82	0.14	3.82	4.03	8.06
Creatinine	4.05	0.23	4.05	4.53	9.06
Sodium	2.77	0.12	2.77	3.04	6.08
Potassium	2.02	0.12	2.02	2.51	5.02
Albumin	2.18	0.16	2.18	2.49	4.98
Total protein	1.62	0.09	1.61	2.48	4.96
Total cholesterol	3.16	0.14	3.16	3.61	7.22

Table 3. % values of expanded uncertainty (U) belonging to analytes and CLIA, RiLi-BAEK and Fraser % allowed total error limits (%TEa) of these values

Analytes	Expanded uncertainty value %	%Tea (CLIA'88)	%Tea RiLi-BAEK	%Tea (Fraser)
Glucose	3.9	10	15	7.9
ALT	6.72	20	21	26.3
AST	3.48	30	21	15.2
Urea	8.06	9	20	15.7
Creatinine	9.06	15	20	6.9
Sodium	6.08	3	5	0.9
Potassium	5.02	15	10	5.8
Albumin	4.98	10	20	3.9
Total protein	4.96	10	10	3.4
Total cholesterol	7.22	10	13	8.6

Discussion

In clinical chemistry, the method's measurement uncertainty has been reduced considerably thanks to automatic measurement methods and reference measurement systems that emerged in the recent years and the most significant innovations have been provided by reproducibility and the daily variation reduction [8]. Measurement uncertainty is defined as a parameter that characterizes the spread of all values that can be reasonably attributed to the measured magnitude and as a parameter that is related to the result of the measurement [11]. More clearly, measurement uncertainty demonstrates the limits of the extent that differs between the first result and the reproduced result of a test. The measured values of the same magnitude vary depending on the measurement. The given number at the end of each measurement certainly includes a doubt [12]. In order for any biochemical test result to be reliable, the result is required to be close to the real value and be reproducible, given together with the uncertainty value, and comparable in national and international environments [1].

In the recent years, a large number of guidelines regarding the calculation of the measurement uncertainty were published [6]. The data obtained from external quality control, internal quality control and method validation studies are at the center of approaches to be used in the calculation of the measurement uncertainty for biochemical/chemical methods [4]. The methods adopted in order to determine measurement uncertainty, the ISO and the Guide to the Expression of Uncertainty of Measurement (GUM) guidelines, are continuously being investigated, in order to provide the most effective guidelines [13]. Because these calculations are complicated and elaborate, their practical applicability is declining [13,14]. In 2012, ''Quantifying Uncertainty in Analytical Measurement'' titled, the Eurachem/CITAC Guide CG 4 was published [15]. It was suggested that the Nordtest guide should be routinely used in clinical laboratories in order to standardize the quantification of measurement uncertainty. Nordtest guidelines, just as other measurement uncertainty calculations, offer an understandable and practical application for the easy practice of measurement uncertainty calculations by the user by using the data belonging to control and validation studies [10].

Errors made on the values close to the medical decisions are of more importance now. Errors mainly result from measurement uncertainty. As a result of this, medical expenses increase, misdiagnoses may occur and even the patient's life may be put at risk [16]. Şentürk et al. reported that when the measurement uncertainty values were added to and subtracted from the results of 7259 patients that were scanned retrospectively, the cannabis decision values in 161 patients and the opiate decision values in 6 patients changed and concluded that decision values may change and thus, it is necessary to conduct verification tests before presenting results [17]. Ustundag et al. investigated blood ethanol levels of 1034 vehicle drivers in an emergency laboratory. The obtained expanded uncertainty was 19.74%. When measurement uncertainty values were included in the results of the 1034 drivers, who were retrospectively screened, it was determined that eight vehicle drivers had results with 95% confidence intervals that exceeded the legal limit 0.50 g/L. Thus, the results of blood ethanol concentration tests that are close to the legal limits should be reported with a confidence interval that contains the true ethanol concentration with its 95% confidence interval (18). Tekce et al. investigated the uncertainty of measurement of serum creatinine concentrations in terms of its effects on the diagnosis of acute kidney injury by making use of the Nordtest Guide. They reported that the uncertainty of measurement for serum creatinine concentrations was a significant factor while diagnosing acute kidney injury correctly. Additionally, it was believed that minimizing the TEA levels of serum creatinine concentrations is necessary for the diagnosing acute kidney injury accurately [19]. İnce et al. reported 3% measurement uncertainty for glucose in their studies and they calculated this value as ± 3.78 mg / dL for the 126mg / dl limit, which is used for diagnosing diabetes [14]. Bal et al. evaluated the measurement uncertainty of biochemical parameters on A, B and C devices and concluded that albumin, creatinine, sodium and total protein values were higher compared %TEa values, which is similar to our findings [4].

In our study, ten parameters that are studies on the biochemical auto analyzer were determined to be lower compared to the ones specified in CLIA and RiLi-BAEK while the calculated %TEa values for albumin, creatinine, sodium and total protein were determined to be higher compared to %TEa values specified in Fraser. According to Fraser, biological variations are the sources of the most important variations that influence the results and by making use of these biological variations, bias and total error limits are calculated [20]. We believe that the reason for our data's inability to meet Fraser's general quality specification is the fact that the aimed limits are low due to the low biological variation in these tests.

In laboratories, different results can be obtained for the same parameter by using different measurement uncertainty models. While calculating the measurement uncertainty in all laboratories, the type of model to be used to calculate the measurement uncertainty and the allowed total error limits for fifteen biochemical tests were determined by the "Notice 2016/18" of the Ministry of Health and were made mandatory. However, the subject of stating the measurement uncertainty to clinicians is still unclear.

The measurement of the samples obtained from the patients can be seen as an entity in the real world and it is impossible to know the "real" value of the measurands. Both MU and TEa theories are associated with traceability. The goal of the TEa concept must be the "Comparability of results across laboratories" [21].

Conclusion

In conclusion, a result of a test or the reliability of a measurement is not effective enough when not evaluated. Laboratories should calculate the measurement uncertainty for each parameter, present results in a way that would not exceed the aimed %TEa values and ensure that clinicians take those factors into consideration while evaluating the patients' results.

Competing interests
The authors have declared that there is no conflict of interest.

Financial Disclosure
This study was not supported by any fund.

References

1. Özmen GG. Klinik biyokimyada ölçüm belirsizliği. Tıpta Uzmanlık Tezi, Yeditepe Ünversitesi Tıp Fakültesi, İstanbul, 2011.
2. Oosterhuis WP, Theodorsson E. Total error vs. measurement uncertainty: revolution or evolution? Clin Chem Lab Med. 2016;54:235-9.
3. JCGM. Evaluation of measurement data – guide to the expression of uncertainty in measurement. JCGM 100:2008, GUM 1995 with minor corrections: Joint Committee for Guides in Metrology. 2008.
4. Bal C, Serdar MA, Güngör OY, et al. Biyokimyasal parmetrelerinin ölçüm belirsizliğinin hesaplanması. Turk J Biochem. 2014;39:538-43.
5. The SAC Accreditation Programme. Technical guide 4 A guide on measurement Uncertainty in medical testing, 2013;1–51.
6. Oğul Y, Şenyurt M, Altınkaynak K, et al. TSH, FT4 ve FT3 testlerinin ölçüm belirsizliğinin değerlendirilmesi. Türk Klinik Biyokimya Derg. 2015;13:89-94.
7. Çelebiler A, Serin H, Güleç D, et al. Klinik biyokimya laboratuvarında ölçüm belirsizliği: pratik uygulama. Türk Klinik Biyokimya Derg. 2011;36:362-6.
8. Theodorsson E, Magnusson B, Leito I. Bias in clinical chemistry. Bioanalysis. 2014;6:2855-75.
9. Richtlinie der Bundesärztekammer zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen. Bundesärztekammer, Berlin, Germany, 2013.
10. Magnusson B, Näykki T, Hovind H et al. Nordtest technical report 537—handbook for the calculation of measurement uncertainty in environmental laboratories, 3nd edition, Nordic Innovation, Oslo, Norway, 2011.
11. 1EURACHEM / CITAC Guide CG4: Quantifying Uncertainty in Analytical Measurement 2nd edition, 2000.
12. Güngör M. Klinik Biyokimyada Ölçüm Belirsizliği. Tıpta Uzmanlık Tezi, Haseki Eğitim ve Araştırma Hastanesi, İstanbul, 2008.
13. Ayyildiz SN. The importance of measuring the uncertainty of second-generation total testosterone analysis. Int J Med Biochem. 2018;1:34-9.
14. İnce FDA, Şentürk BA, Kap S, et al. Klinik Biyokimya Laboratuvarında Glukoz Parametresi İçin Ölçüm Belirsizliği Değerlendirilmesi. Türk Klinik Biyokimya Derg. 2007;5:1-5.
15. Ellison S, Williams A. EURACHEM/CITAC Guide CG 4: Quantifying uncertainty in analytical measurement. 2012;4–6.
16. Aytekin M, Cevlik T, Emerk K. Describing an ideal model for calculating the uncertainty of measurements in a clinical laboratory. Clin Biochem. 2009;42:321-2.
17. Şentür B.A, Kaplan Y.C, Yiğitbaşı T, et al. Esrar (cannabis) ve opiyat testleri için ölçme belirsizliği değerinin saptanması ve klinik karar değerine etkisi. Turk J Biochem. 2013;38:181-5.
18. Ustundağ U, Huysal K. Measurement uncertainty of blood ethanol concentration in drink-driving cases in an emergency laboratory. Biochem Med. 2017;27:030708.
19. Tekce BK , Tekce H , Aktas G, et al. The role of the uncertainty of measurement of serum creatinine concentrations in the diagnosis of acute kidney injury. Renal Failure. 2016;38:305-10.
20. Fraser CG. Biological variation: from principle to practice, AACC Press, Washington 2001;1-143.
21. Oosterhuis WP, Bayat H, Armbruster D, et al. The use of error and uncertainty methods in the medical laboratory. Clin Chem Lab Med. 2018;56:209-19.