원저
Lab Med Online
Vol. 7, No. 2: 66-72, April 2017
https://doi.org/10.3343/lmo.2017.7.2.66

임상화학 LMO

Beckman Coulter AU5800를 이용한 용혈, 고빌리루빈혈증, 고지방혈증에 의한 간섭영향 HIL 인덱스의 수정안 제안

Proposal of Modified HIL-indices for Determining Hemolysis, Icterus and Lipemia Interference on the Beckman Coulter AU5800 Automated Platform

임용관 · 차영주
Yong Kwan Lim, M.D., Young Joo Cha, M.D.

중앙대학교 의과대학 진단검사의학교실
Department of Laboratory Medicine, Chung-Ang University College of Medicine, Seoul, Korea

Background: The amount of interference due to hemolysis, bilirubin, and lipemia can be measured on the AU5800 autoanalyzer (Beckman Coulter, USA) by spectrophotometry. This is reported as semi-quantitative indices, specifically H-index, I-index, and L-index, respectively. In this study, we evaluated the impact of interference using chemistry assays and established the concentration of interfering substances and HIL-index above which analytically significant interference exists, according to CLSI guidelines C56-A and EP7-A2.
Methods: Pooled sera including different concentrations of analytes were prepared and mixed with hemoglobin, bilirubin, or Intralipid. These samples were then tested for 35 clinical chemistry analytes by AU5800 and the bias based on interferent concentrations was computed. The interferent concentration above which significant interference exists was calculated from the 50% within-subject biological variation (desirable analytic goal), and the corresponding index was assigned.
Results: Among 35 items evaluated, interference was detected for 12 analytes by hemoglobin, 7 analytes by bilirubin, and 12 analytes by Intralipid. We proposed HIL-index$_1$ and HIL-index$_2$ for each analyte according to 2 different medical decision levels. HIL-index$_1$ and HIL-index$_2$ were considered more reasonable criteria than the HIL-index from the manufacturer's technical document (HIL-index$_{TD}$). This is because HIL-index$_{TD}$ was empirically set to 5% or 10%, and had a wide tolerance range, which was not sufficient to reflect the presence of interference, compared to HIL-index$_1$ and HIL-index$_2$.
Conclusions: We have demonstrated hemoglobin, bilirubin, and Intralipid interferences according to CLSI guidelines using the desirable analytic goal. Our results provide applicable information for Beckman Coulter automated chemistry analyzers.

Key Words: Interference, Hemolysis, Icterus, Lipemia, Chemistry, AU5800

INTRODUCTION

Interfering substances are considered a significant source of error in clinical laboratory measurements [1]. Such interference may be a leading cause of inappropriate treatment or misdiagnosis. While precision is periodically checked using internal controls and accuracy is verified by comparison to reference materials or external quality assessment, erroneous results due to interference from endogenous or exogenous substances are subjectively evaluated or overlooked by clinical laboratories. It has long been recognized that hemolysis, bilirubin, and lipids (HIL) are the most common and most significant sources of error in laboratory medicine [2]. Due to their spectral characteristics, these substances can cause optical interference. Moreover, inherent chemicals such as potassium in the cytoplasm of erythrocytes can disrupt the results of measured components.

Previously, inspection of individual specimens by the naked eye was routinely applied as the system for detecting and reporting HIL interference. However, visual interpretation of these inter-

Corresponding author: Young Joo Cha
Department of Laboratory Medicine, Chung-Ang University College of Medicine, 102 Heukseok-ro, Dongjak-gu, Seoul 06973, Korea
Tel: +82-2-6299-2720, Fax: +82-2-6298-8630, E-mail: chayoung@cau.ac.kr

Received: July 4, 2016
Revision received: August 17, 2016
Accepted: August 30, 2016

This article is available from http://www.labmedonline.org

eISSN 2093-6338

ferents is subjective and has demonstrated little agreement between the actual concentration of each interferent and the assigned grade of turbidity, hemolysis, or icterus [3]. To overcome these disadvantages, automated HIL-indices were introduced and adopted in clinical laboratories. The Beckman Coulter AU5800 (Beckman Coulter, Brea, CA, USA) is a recently introduced chemistry analyzer equipped with HIL systems that can detect and semi-quantify the interference of hemolysis, icterus, and lipemia. This analyzer can quantify the serum condition by spectrophotometric measurements using several wavelengths. It also presents the interfering substances as index values according to mathematical algorithms.

Although several studies have evaluated the interfering effects of hemolysis, icterus, and lipemia [4-6], there are only a few documents specifying the proper methods to perform interference studies [2]. In 2012, the Clinical and Laboratory Standards Institute (CLSI) published guidelines for HIL-indices to enhance the accuracy of reported patient test reports [7]. This document provided detailed protocols on establishing HIL-indices, estimating interference effects of HIL, and reporting interference effects of HIL. Therefore, the aim of our study was to evaluate the interference effect of hemolysis, icterus, and lipemia on routine chemistry assays and the performance of AU5800 HIL systems according to the CLSI guidelines C56-A and EP7-A2 [7, 8]. In addition, based on the results of our interference study, we established the HIL-index for each analyte and assessed the practicality of the CLSI guideline for clinical laboratories.

MATERIALS AND METHODS

1. Chemistry Analyzer

The Beckman Coulter AU5800 clinical chemistry analyzer (Beckman Coulter, Brea, CA, USA) is a novel fully automated analytical platform designed for the analysis of routine chemistry assays, immunoassays, and therapeutic drugs. The AU5800 analyzer is also able to detect hemolysis, icterus, and lipemia in samples. It is programmed to generate semi-quantitative index values as a measure of the concentration of these interfering substances (Table 1). Patient samples are diluted with the LIH reagent and the absorbance is measured at 6 unique wavelengths: 410/480 nm and 600/800 nm for hemolysis, 480/570 nm and 600/800 nm for icterus, and 660/800 nm for lipemia. This spectrophotometric method estimates the levels of hemoglobin, bilirubin, and lipid, which have distinct absorption spectra. If one or more chromogen in the potentially interfering concentration is present in a sample, semi-quantitative index values are reported along with the results of the sample.

Table 1. The relationship between the concentration of the interfering substance and the corresponding HIL-index, according to manufacturer's specification

HIL-index	Hemoglobin (mg/dL)	Bilirubin (mg/dL)	Intralipid (mg/dL)
0	< 50	< 2.5	< 40
1	50-99	2.5-4.9	40-99
2	100-199	5.0-9.9	100-199
3	200-299	10-19.9	200-299
4	300-500	20-40	300-500
5	> 500	> 40	> 500

2. Measured Analytes

The following 35 analytes were measured: total protein, albumin, total bilirubin, direct bilirubin, blood urea nitrogen (BUN), uric acid, alkaline phosphatase (ALP), inorganic phosphorous (IP), magnesium, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), lipase, phospholipid, glucose, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), γ-glutamyltransferase (GGT), total calcium, amylase, creatine kinase (CK), sodium, potassium, chloride, iron, unsaturated iron binding capacity (UIBC), total cholesterol, bicarbonate, C-reactive protein (CRP), high-sensitivity C-reactive protein (hs-CRP), ethanol, ammonia, and ketone bodies (KB).

3. Interference Testing

According to the CLSI document EP7-A2 [8], we evaluated the effects of hemolysis, icterus, and lipemia by adding hemoglobin, bilirubin, and Intralipid to serum pools with known analyte concentrations. Interference testing was performed at two different medical decision levels of the analytes. Pooled sera were prepared as test samples, and all were inspected by the naked eye to ensure the absence of interferents, except for pooled sera containing high bilirubin and lipid concentrations. To establish the interference effects of hemolysis, icterus, and lipemia/turbidity, 24 different serum pools including different concentrations of analytes were prepared and mixed with hemoglobin-, bilirubin- or Intralipid-stock solutions. Hemoglobin-stock solution was prepared by adding purified hemoglobin (Sigma-Aldrich, MO, USA) to distilled water. Bilirubin powder (Sigma-Aldrich, MO, USA) mixed with di-

Table 2. Average concentration of tested analytes and desirable bias cut-off criteria for interference

Analyte	Unit	Average concentrations		$B_{cut-off}$ (%)	Analyte	Unit	Average concentrations		$B_{cut-off}$ (%)
		Level 1	Level 2				Level 1	Level 2	
Total protein	g/dL	7	8.6	1.4	LDH	IU/L	146.8	332.3	4.3
Albumin	g/dL	4.1	4.7	1.6	GGT	IU/L	33.2	201.5	6.7
Total bilirubin	mg/dL	0.6	12.7	10.9	Total calcium	mg/dL	9	9.6	1.1
Direct bilirubin	mg/dL	0.2	8.2	18.4	Amylase	IU/L	65	363.3	4.4
BUN	mg/dL	18	45	6.1	CK	IU/L	62.2	1197.5	11.4
Uric acid	mg/dL	4.9	7.5	4.3	Sodium	mEq/L	143.8	148.8	0.3
ALP	IU/L	55.9	300.7	3.2	Potassium	mEq/L	4.5	4.9	2.3
IP	mg/dL	3.8	3.9	4.1	Chloride	mEq/L	106.2	115.7	0.6
Magnesium	mg/dL	2.1	2.7	1.8	Iron	μg/dL	90.5	147.2	13.3
Triglyceride	mg/dL	108.7	547.8	10.0	UIBC	μg/dL	209.5	384	10*
HDL	mg/dL	42.7	67.5	3.7	Total cholesterol	mg/dL	176	279.7	3.0
LDL	mg/dL	105.2	180.3	3.9	Bicarbonate	mmol/L	16.1	27.6	2.0
Lipase	IU/L	24.5	427	16.1	CRP	mg/L	9.8	154.5	21.1
Phospholipid	mg/dL	188	262.5	3.3	hs-CRP	mg/L	10.6	30.4	24.9
Glucose	mg/dL	128	204.7	2.8	Ethanol	mg/dL	7.6	87.4	10*
Creatinine	mg/dL	1.2	2.9	3.0	Ammonia	μg/dL	200	394	10*
AST	IU/L	22.7	269.5	6.2	KB	μmol/L	85.5	479	10*
ALT	IU/L	9.5	83.2	9.7					

$B_{cut-off}$: Cut-off bias calculated based on the desirable analytic goal.
*Arbitrarily set to 10% owing to a lack of within-subject biological variation data.

methyl sulfoxide was used to prepare the bilirubin-stock solution. Intralipid (20%) (Sigma-Aldrich, MO, USA) was used as the stock solution for evaluating the lipemia/turbidity effect. Although Intralipid was not equivalent to the lipemic effect in vivo, it has been considered the best substitute for interference studies [9]. To determine the relationship between interferent concentration and the magnitude of interference, eight samples with increasing concentrations of interferent were prepared by mixing with the pooled sera and stock solutions. To minimize the potential interference due to the reduction of an endogenous substance, the stock solution was diluted to no more than 5% of the pooled serum. Each sample was measured over 2 days, with one run per day. The percent of change was calculated from baseline concentrations. This study was performed with the approval of the institutional review boards of Chung-Ang University Hospital.

4. Acceptability Criteria for Evaluating the Interference Effects

We defined analytically significant interference when the bias in the presence of the interfering substance differed by more than the desirable analytic goal. The desirable analytic goal was calculated as one-half of the average biological variation, and was termed the cut-off bias ($B_{cut-off}$) to evaluate the interference effect. This parameter has also been called the tolerable analytical variation, and has been used to generate quality specifications [10, 11]. To calculate $B_{cut-off}$, the within-subject biological variation (CV_w) was adopted from the Westgard QC website [12]. If there were no available data for CV_w, $B_{cut-off}$ was arbitrarily set to 10%. Table 2 summarizes the tested concentrations of all analytes and their $B_{cut-off}$. The concentration of interferents above which there was clinically significant interference was termed the clinical cut-off concentration ($C_{cut-off}$). The corresponding index for this concentration was called the cut-off index; H-index for hemoglobin, I-index for bilirubin, and L-index for Intralipid.

5. Statistical Analysis

Statistical analysis of the correlation between the interferent concentration and the magnitude of interference was performed using the linear least square regression analysis. All statistical analyses were performed using SigmaPlot 12.0 (Systat Software Inc., CA, USA).

RESULTS

The relationship between the concentration of the three interferents and the reported HIL-indices is summarized in Table 3. Al-

https://doi.org/10.3343/lmo.2017.7.2.66

Table 3. Averages of reported H-, I-, and L-index according to interferent concentrations

Tested hemoglobin concentration (mg/dL)	Averages of H-index	Tested Bilirubin concentration (mg/dL)	Averages of I-index	Tested Intralipid concentration (mg/dL)	Averages of L-index
0	0	0	0	0	0
30	0.04	2	1.13	20	0.27
60	0.88	4	2.04	70	1.08
120	1.52	8	2.92	150	2.00
240	2.02	16	3.65	250	2.58
480	4.04	32	4.10	400	3.96
720	4.96	48	5	600	4.13
960	5	64	5	1,000	5

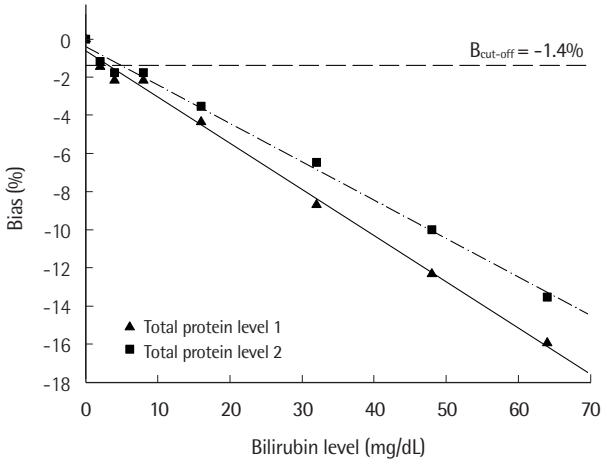

Fig. 1. Bilirubin interference in the measurement of total protein. Analyte bias was plotted by linear regression analysis, and the interferent concentrations at which interference began were calculated with the desirable analytic goal ($B_{cut-off}$).

though all of the three indices did not precisely match the corresponding interferent concentrations, an increasing trend in the indices was observed with increased concentrations of interferent.

Fig. 1 shows a representative interferograph of bilirubin interference in total protein measurement. The concentration of interferent was plotted on the X-axis and the bias of each analyte was plotted on the Y-axis. A line of best fit was drawn based on linear least squares regression analysis. The cut-off concentration for total protein calculated from half of the CV_w was 1.4% ($B_{cut-off}$), and the bilirubin concentration at which interference began was 3.0 mg/dL (I-index=1) for level 1 and 4.7 mg/dL (I-index=1) for level 2. All analyte levels were evaluated in the same manner, and HIL-indices for each inteferent were assigned.

Tables 4, 5, and 6 summarize significant interferences, HIL-indices calculated from technical documents (HIL-index$_{TD}$), and established HIL-indices for 2 levels of each analyte (HIL-index$_1$ and HIL-index$_2$). Most of the analytes did not exhibit interference from hemoglobin, bilirubin, and lipemia, with few exceptions: 12 analytes by hemoglobin, 7 analytes by bilirubin, and 12 analytes by lipemia. Total protein, albumin, IP, magnesium, AST, ALT, LDH, iron, and total cholesterol exhibited positive interference by hemoglobin while ALP, GGT, and UIBC decreased with the hemoglobin increment (Table 4). Specifically, interference was observed with magnesium at very low concentrations of hemoglobin (H-index, 0). In addition, most analytes were affected by lower hemoglobin concentrations compared to the H-index$_{TD}$ calculated from technical documents provided by the manufacturer. As expected (Table 5), total and direct bilirubin levels were increased with the addition of purified bilirubin, and magnesium. Moreover, ammonia also falsely increased. A decrease in total protein, creatinine,

Table 4. Items affected by hemoglobin; comparing the H-index$_{TD}$ obtained with AU5800 and the H-index calculated in this study for each analyte

Analyte	H-index$_{TD}$	H-index$_1$	H-index$_2$
Increasing effect			
Total protein	4	1	2
Albumin	4	2	3
IP	4	5	4
Magnesium	2	0	0
AST	NS*	1	4
ALT	5	2	5
LDH	NS*	2	2
Iron	2	0	1
Total cholesterol	5	3	5
Decreasing effect			
ALP	5	3	5
GGT	3	2	4
UIBC	3	1	2

H-index$_{TD}$: H-index from the technical document provided by the manufacturer.
H-index$_1$: H-index calculated from the level 1 sample in this study.
H-index$_2$: H-index calculated from the level 2 sample in this study.
*Not specified in the technical document.

Table 5. Items affected by bilirubin; comparing the I-index$_{TD}$ obtained with AU5800 and the I-index calculated in this study for each analyte

Analyte	I-index$_{TD}$	I-index$_1$	I-index$_2$
Increasing effect			
Total bilirubin	NS*	0	0
Direct bilirubin	NS*	0	0
Magnesium	4	2	3
Ammonia	NS*	5	5
Decreasing effect			
Total protein	4	1	2
Creatinine	4	4	4
Total cholesterol	2	1	1

I-index$_{TD}$: I-index from the technical document provided by the manufacturer.
I-index$_1$: I-index calculated from the level 1 sample.
I-index$_2$: I-index calculated from the level 2 sample.
*Not specified in the technical document.

Table 6. Items affected by Intralipid; comparing the L-index$_{TD}$ obtained with AU5800 and the L-index calculated in this study for each analyte

Analyte	L-index$_{TD}$	L-index$_1$	L-index$_2$
Increasing effect			
Albumin	5	1	3
IP	5	3	5
Magnesium	5	1	1
Triglyceride	NS*	0	1
Phospholipid	NS*	1	3
Iron	2	2	5
Ammonia	NS*	3	5
Decreasing effect			
Total protein	5	2	4
Uric acid	5	4	5
HDL	5	2	4
LDL	NS*	1	2
Creatinine	5	0	5

L-index$_{TD}$: L-index from the technical document provided by the manufacturer.
L-index$_1$: L-index calculated from the level 1 sample.
L-index$_2$: L-index calculated from the level 2 sample.
*Not specified in the technical document.

and total cholesterol by bilirubin interference was observed. For samples with added Intralipid (Table 6), the results for albumin, IP, magnesium, triglyceride, phospholipid, iron, and ammonia showed positive interference by Intralipid, whereas total protein, uric acid, HDL, LDL, and creatinine were inversely affected by Intralipid. Triglyceride and phospholipid levels were increased as expected; however, HDL and LDL decreased. Total cholesterol was not affected by Intralipid, but was negatively affected by bilirubin. Total protein was affected by all three interferents, of which hemoglobin had a positive effect, and bilirubin and Intralipid had negative effects. Magnesium also exhibited positive interference by all three interferents. Ammonia was positively affected, whereas creatinine was negatively affected by both bilirubin and Intralipid. Albumin and IP were positively affected by both hemoglobin and Intralipids, and uric acid was negatively affected by Intralipid. For most analytes, we found that the HIL-index calculated in this study was lower than those described in the evaluated technical documents.

DISCUSSION

A major goal of clinical laboratories is to produce accurate and precise results. However, endogenous compounds that affect chemical measurements in various ways are considered a significant source of error. Particularly, hemolysis, icterus, and lipemia may be the most common interferents related to sample integrity [5]. Therefore, it has been crucial for a long time for clinical laboratory staff to visually inspect samples owing to the possibility of interference caused by these substances. However, visual inspection is subjective and does not accurately detect the presence of endogenous interferents [13]. An automated detection system for these interferents, the HIL system, provides an objective and consistent method for estimating sample quality. With this system, one can easily identify the sample integrity issues caused by hemolysis, icterus, and lipemia with semi-quantitative estimates. In this study, although the reported semi-quantitative HIL-index of the AU5800 system did not perfectly match the manufacturer's specifications, it was sufficient to reflect the presence of interfering substances in the samples tested. However, we suspected that the difference between concentrations of interferents and reported HIL-indices could be originated from the inaccurate preparation of pooled serum samples likely spiked with interferents.

Although manufacturers provide information about interfering substances, laboratories should consider verifying HIL-indices after implementation in laboratory practice. The CLSI guideline C56-A is one of a few guidelines that address the HIL system. It provides practical protocols for establishing and validating the HIL-index [7]. With this guideline, clinical laboratories can easily estimate the effects of interfering substances and obtain enough information to create a policy for handling samples with a high risk of unreliable results. However, limitations in resources and budgets force clinical laboratories to rely on documents provided by manufacturers. This could give rise to inaccurate results, since the HIL parameters are based on spectrophotometric measurements

https://doi.org/10.3343/lmo.2017.7.2.66

that are subject to drift and failure. This study therefore serves as a valuable example about establishing and validating the HIL-index for automated chemistry analyzers. We expect that our results can be applied by all laboratories that use AU5800 or other Beckman Coulter automated chemistry analyzers.

When introducing an HIL system, it is critical to determine how much bias is clinically significant. In the CLSI guideline C56-A, the acceptability criteria are derived from the biological variation of the analyte and the precision of the measurement system [7]. According to this guideline, the acceptability criteria are calculated from pooled variation ($\sqrt{(within\text{-}subject\ variation)^2 + (precision)^2}$) multiplied by 1.96, which is the approximate value of the 97.5 percentile point of the normal distribution. With this formula, the acceptability criteria would be approximately 2-3 times higher than the precision when biological variation is equal to or lower than the precision. This approach is statistically reasonable, and these criteria have been widely applied [6, 10]. However, the within-subject variation is generally much larger than the analytical imprecision. Therefore, the acceptability criteria described in the CLSI guideline C56-A is approximately twice as much as the within-subject variation [14]. This indicates that more than 50% bias could be allowed in some analytes. In the CLSI guideline C56-A, the acceptability criteria for direct bilirubin and lipase were calculated as 72.3% and 63.3%, respectively. Although this approach is statistically reasonable, no clinical laboratory director can easily apply these acceptability criteria to ensure accurate and precise results with interfering substances.

As an alternative, desirable analytic goals can be used as appropriate interference criteria. The criteria are facilitated by a simple calculation consisting of 50% within-subject variation and easy access to the database on biological variation [12, 15]. Compared to the cut-off concentrations calculated in the CLSI guideline C56-A, desirable analytic goals were generally less than half of the previously specified cut-off concentrations. With this criterion, information that is more robust can be obtained about the existence of interfering substances in samples, which would better prevent pre-analytical errors in many clinical laboratories. However, the application of desirable analytic goals also has limitations due to lack of knowledge concerning biological variation. Although we empirically applied 10% as the criteria for the analytes in this study, there is no evidence that 10% bias originating from interferents is allowable. In addition, the allowable interference is set to 5% or 10% in batches obtained from manufacturers [16]. Since a variety of applicable criteria exist, each laboratory should carefully select the appropriate acceptability criteria depending on its needs, because there is no general consensus on which criteria is most suitable for specific analytes [17]. However, it should be noted that more stringent quality goals would be advantageous in reflecting sample quality.

There are some limitations in this study. First, due to the use of purified materials such as commercially available hemoglobin and Intralipid, our experiments might not be representative of troublesome specimens encountered in laboratories. Despite having the advantage of spectral interference, purified hemoglobin is not a suitable alternative for improper blood sampling through the induction of whole blood lysis. The hemolyzed samples should be prepared by mechanical hemolysis similar to that in other interference testing methods [18] to identify the 'true' hemolysis interference in the clinical chemistry assay. In addition, Intralipid is not an interchangeable substitute for 'real' lipemic interference due to the different photometric response to synthetic fat emulsion from physiological lipemia. As expected, a previous study demonstrated different characteristics of interference between lipemic samples and Intralipid-supplemented samples [19]. In this study, the effect of Intralipid varied depending on the type of lipids involved. Triglyceride and phospholipid were increased with spiking Intralipid containing these analytes. However, HDL and LDL decreased due to the volume effect of Intralipid [20].

In this study, we evaluated the effects of hemolysis, icterus, and lipemia on clinical chemistry assays with AU5800, and established HIL-indices for each analyte according to the CLSI guideline. These HIL-indices can provide an effective screening method for the verification of specimen quality. However, the interference effect could be interpreted with various criteria. Furthermore, the amount of interference is clinically significant when adopting the HIL-index in the clinical laboratory.

요 약

배경: 용혈, 고빌리루빈혈증, 고지방혈증에 의한 간섭영향은 자동화 장비의 분광광도계를 이용하여 측정될 수 있고, AU5800 (Beckman Coulter, USA)는 H-, I-, L-인덱스를 통해 이러한 간섭물질의 영향을 반정량적으로 보고해 준다. 저자들은 CLSI 가이드라인에 따라, 용혈, 고빌리루빈혈증, 고지방혈증에 의한 간섭이 임상화학검

사에 미치는 영향을 평가하였고, 검사결과에 영향을 미치기 시작하는 간섭물질의 농도와 그에 따른 반정량적 인덱스를 산정하였다.
방법: 다양한 농도의 측정물질을 포함하는 풀링된 혈청에 헤모글로빈, 빌리루빈, Intralipid를 첨가하였다. 그리고 AU5800을 통하여 35종의 측정물질을 검사한 뒤, 간섭물질의 농도에 따른 측정물질 농도의 변화를 확인하였다. 간섭효과에 대한 허용 바이어스를 개체 내 변이의 절반(desirable analytic goal)으로 설정하였고, 이에 따라 간섭효과가 나타나기 시작하는 간섭물질의 농도와 이에 상응하는 반정량적 인덱스(H-, I- L-인덱스)를 산출하였다.
결과: 간섭효과를 측정한 35검사항목 중 혈색소에 영향 받는 항목은 12항목, 빌리루빈에 영향 받는 항목은 7항목, 지질에 영향 받는 항목은 12항목이었다. 각 검사항목에 대하여 서로 다른 두 농도에서 측정한 HIL 인덱스를 제시하였는데, 이는 경험적으로 허용 바이어스를 5% 내지 10%로 높게 정하여 제시하는 기술문서상의 반정량적 인덱스에 비해 생물학적 변동폭의 절반을 허용 목표로 설정하여 보다 합리적으로 간섭효과를 반영할 수 있었다.
결론: 본 연구는 CLSI 가이드라인에 따라 용혈, 고빌리루빈혈증, 고지방혈증이 AU5800의 측정항목에 미치는 간섭효과를 확인하였고, 생물학적 변동폭의 절반을 허용 바이어스로 하여 반정량적인 인덱스를 산출하였으며, 이는 베크만 쿨터사의 자동화 임상화학 검사장비에 적용할 수 있을 것으로 기대된다.

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https://doi.org/10.3343/lmo.2017.7.2.66