Original Article

Assessment of Serum Indices Implementation on Roche Cobas 6000 Analyzer

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Abstract

Background: Hemolyzed, lipemic and icteric samples which can be determined by naked eye can cause erroneous results and wrong diagnosis and treatments, so they are considered to be unsuitable and thus rejected. However, visual evaluation is subjective and is not sufficiently reliable. The aim of this study was to evaluate efficiency and advantages of serum index program on the basis of test parameters for detection of visually unrecognized interferences by analysing the samples in an automated system that include a serum index program.

Methods: After examining through the naked eye, 717 serum samples which were decided to not be hemolyzed, lipemic and icteric were picked out for the study. These samples were analyzed on Roche Cobas 6000 autoanalyzer for 23 different parameters which were known to be most affected from interferences. At the same time, serum indices were also analyzed using Roche serum index application program.

Results: In 108 of 717 serum samples interference that previously could not be detected by naked eye was detected. 102 of these were hemolysis, 4 were lipemia and 2 were icterus. Tests that were affected by hemolysis were creatine kinase isoenzyme MB(CK-MB), lactate dehydrogenase (LDH), aspartat aminotransferase (AST), total bilirubin, direct bilirubin, unsaturated iron binding capacity (UIBC) respectively.

Conclusions: In detection of hemolytic, icteric and lipemic samples, visual detection is not reliable and automatized systems that gives serum indices results based on the test parameters should take the place of visual detection as a cheap and fast way of accelerating the standard laboratory process and making it easier.

Keywords: Interferences, preanalytic error, serum indices, Roche Cobas

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Introduction

Laboratory data can be affected by many variables. A number of diseases result in increased amounts of chromogens such as bilirubin or hemoglobin, or lipemic particles, which increase the turbidity. These chromogens interfere with many photometric assays. However, this interference can be quantified by means of serum index measurements. When information related to analytical interferences is not reported with patient test results, clinicians may interpret test results incorrectly and make unsuitable procedure related to patients. Interference affecting the test results should be understood well to give proper clinical decisions. When interferences affecting the blood or other samples are properly determined and standardized, clinical decisions depending on laboratory test results can be given more accurately (1,2). While analytical standards are being developed by quality assessment criteria, there are shortcomings in the development of standards related to the preanalytical phase. Recently, some recommendations related to definition of the optimal sample volume, use of anticoagulant and stabilizer, sample collection, transport and storage, icteric, lipemic, and hemolyzed samples prevention have been published (3). Total laboratory process consists of preanalytical, analytical and postanalytical phases. Preanalytic phase is one of the most important components of the medical laboratory. Quality control studies should be made for all analytical phases to provide the precision and accuracy of laboratory test results. Despite the technological advances in laboratory automation devices and developments in quality control programs, laboratory errors still occur. Prenalytical phase is the process in which the vast majority of laboratory errors happen (3,4). Plebani et al reported that the manuscript distribution of laboratory errors is as such: 68.2% in preanalytical, 13.3% in analytical and 18.5% in postanalytical phase. Preanalytical phase includes all of the various procedures before measurement of a sample. Preanalytical factors include patient related variables (age, sex, diet, stress, medication…), sample collection (blood collection technique, sample volume, anticoagulant type…), sample transport and sample preparation procedures. Before analysis, detection of inappropriate sample plays an important role in the prevention of errors because laboratory errors usually emerge in preanalytical phase and they can lead to further, inappropriate investigation and treatments. In addition, the samples which are rejected due to analytical interferences will lead to loss of time, labour and supplies, leading to increases in cost (3,5).

Up to now, medical laboratories have taken a "judgment inspection" approach to endogenous interferences; the operator decides whether the sample is appropriate or inappropriate. If an abnormal result is obtained, the sample is inspected for visible interferences. Thus, judgment inspections can only detect errors after they have been made and identified. Manuel inspection may be performed on every sample before analysis or inspecting samples that produce "suspect" results. This is very time consuming. In addition a normal result does not create suspicion. When serum indices are produced by the instrument, consistent evaluations are made and remove the potential for human error and save operator time. The costs involved in repeating "out of limit" results due to interferences are reduced. The serum index result reported with the test results enables the operate to acknowledge the presence of interfering substances as the potential cause of the abnormal result and removes need to rerun the sample, thus reducing costs. Glick interferographs are produced for all assays. This is an easily understandable graphical display of the interference data showing the deviation from the original result caused by the interferent. The level of interference producing a clinically significant difference is indicated in Roche pack insert (6-8). In this study, we aimed to evaluate the effectiveness of current serum indices implementations with existing automated systems for detection of interferences which are unrecognized visually and to assess their positive and practical advantages for routine laboratory processes.

Materials and Methods

Study Design:

This observational study was performed in Kutahya Dumlupinar University Evliya Celebi Education and Research Hospital in June 2013. Evliya Celebi Education and Research Hospital has 750 bed capacity and 40 medical departments. The study was carried out in accordance with Declaration of Helsinki.

Sample Collection and Preparation:

Patient samples which were received at the laboratory for routine analysis were used in this study. Fasting venous blood samples were collected by using Vacuette® Standard tube holder and Vacuette® 21-gauge, 0.80×38 mm multisample needle (Vacuette®, Greiner Bio-One, Kremsmunster, Austria) in the morning during a week. Blood samples were drawn into 8 mL serum gel seperator tubes (Vacuette®Tube Serum Gel Separator Clot Activator 8 mL, Greiner Bio-One, Kremsmunster, Austria)(Ref.No.455071, Lot.No.A120600Y). Blood samples were centrifuged at 3000 g for ten minutes. After centrifugation, serum samples were inspected visually by laboratory technicians during a week. Visual examination was done by two laboratory technicians who were informed about the study. Visual examination was performed according to our standardized colored photos and they made a consensus about the doubtful samples according to this photos. Consequently, 717 patient samples which were decided visually to not to include any interferences were reserved for study. These samples freshly analyzed without delay.

Measurement of Test Parameters:

Twenty three different test parameters that known to be most affected by interferences were analysed. All of the tests were analysed on Roche Cobas 6000 autoanalyzer (Roche Diagnostics, Mannheim, Germany) with the original reagents (Roche Diagnostics GmbH D-68298 Mannheim, Germany). Analysed test parameters and methods of analyses are shown in table 1. While these parameters were being analyzed, serum indices were also examined at the same time.

Description of Roche Serum Index Programme:

Serum indices are calculations of absorbance measurements that provide semiquantitative representation of icterus, hemolysis or lipemia (turbidity) levels present in patient samples. For this purpose, Roche Serum Index Gen2 (SI2) application program was used. This program works based on test parameters and gives index results for each test parameters. Working principle of Roche serum indices application is as follows: For measuring serum indices, the analyzer takes an aliquot of the patien sample, dilutes it with 0.9% NaCl and then measures the absorbances at three pairs of wavelengths. For measurement of lipemia, wavelengths of 700/660 nm are used because this range is free from influence by hemolysis and icterus. Hemolysis is measured at 600/570 nm. Icterus is measured at 505/480 nm. To obtain the serum indexes L, H, and I from the sample's absorbances, the system uses the certain formulas. After serum indices are measured, autoanalyzer compares them with the hemolysis (H), icterus (I) and lipemia (L) limits given in each individual test application. Once the serum indexes are determined, refer to the application's package insert to assess the results. This indicates the index up to which potential interference is within the Roche Diagnostics specification or when the hemolysed, icteric, or lipemic sample may not be used with the respective application. Potential interference below these limits is considered clinically irrelevant. Upper limits for serum indexes can be defined individually for each test. Limit values are loaded with the application. If measured values are higher than specified limits of the individual tests, the analyzer issues alarms for the measured results. For example; the application albumin is programmed with a L index limit of 200 and if the obtained L index is greater than 200, a serum alarm is issued. Therefore a serum data alarm is attached to the result. If an index value is higher than a

parametre's limit, an index warning ">" is put next to that parameter. Each report contains a note indicating the appearance of the sample. Serum indices are represented as I.H. for hemolysis, I.L. for lipemia and I.I. for icterus. The hemolysis index, I.H, is reported in hemolysis units that are linear, up to1000 mg/dL, and semi-quantitative. For example, a hemolysis index of 500 is equivalent to a known hemoglobin concentration of approximately 500 mg/dL. The lipemia index, I.L, is reported in lipemia units corresponding to mg/dL of Intralipid® (Kabi-Pharmacia, Inc.), an artificial lipid material. These units are linear, up to 2000 mg/dL, and semi-quantitative. For example, an L index of 1000 is equivalent to a 1000 mg/dL Intralipid solution. Hence, the L index provides an estimate of sample's turbidity, not its concentration of triglycerides. The icterus index, I.I, is reported in icterus units that are linear, up to 60 mg/dL, and semi-quantitative. For example, an icterus index of 20 is equivalent to a known unconjugated bilirubin concentration of approximately 20 mg/dL. List of interferences based on serum indices are shown in table 1. Roche conducts the interference studies according to guidelines of The National Committee for Clinical Laboratory Standarts (NCCLS) (6).

Results

In present study, while interferences were detected in 108 of 717 patient samples by using Roche Serum Index Gen2 (SI2), remaining 609 samples did not have any nfluence and were normal. Hemolysis was detected in 102 samples, lipemia was detected in four samples and icterus was detected in only two samples. The percentages of interferences in all samples were shown in figure 1. Percentage distribution of hemolysis was 14.22% in total patient samples and 94.44% in interfered samples. Percentage distribution of lipemia was 0.55% in total patient samples and 3.70% in interfered samples. Percentage distribution of icterus was 0.27% in total patient samples and 1.85% in interfered samples. The percentages of interferences in samples that detected interferences were shown in figure 2. While some of the tests that we analysed were affected by interference, some tests were not. Tests which were affected by hemolysis were creatine-kinase MB (CK-MB), lactate dehydrogenase (LDH), aspartat aminotrans ferase (AST), total bilirubin (T.BIL), direct bilirubin (D.BIL), and unsaturated iron binding capacity (UIBC). In the other parameters, the interference due to hemolysis was not observed because, measured values of this parameters were not higher than specified limits of them. In interfered samples, percentage distributions of the affected tests by hemolysis interferences were shown in figure 3. Hemolysis index (I.H.) values of affected samples by hemolysis were lowest 11 and highest 181 and these values were presented in test result reports as warning in test results. When all of the samples affected by hemolysis were evaluated in terms of I.H. value, number and type of affected test parameters were seen to differentiate depending on the I.H. value. Distribution of affected tests according to I.H. value were shown in table II. Quantitative comparisons of affected test results according to normal reference ranges or above reference ranges shown in figure 4.

Table 1. Analysed test parameters, methods of analysis and list of interferences based on serum indices for serum.

	Index L	**Index H**	**Index I**	**Icteric Index as conj. bilirubin**	**Icteric Index as unconj. bilirubin**	**Hemolytic Index as Hb**	**Lipemic Index as Intralipid ®**	
Analyte	**Method**				mg/dL	mg/dL	mg/dL	Turbidity
Albumin	Colorimetric,Bromcresol green	550	1000	60	60	60	1000	550
ALP	Colorimetric,PNPP IFCC	2000	200	60	60	60	200	2000
ALT	UV without P5P	150	200	60	60	60	200	150
Amylase	Colorimetric,enzymatic,EPS	1500	500	60	60	60	500	1500
AST	UV without P5P	150	40	60	60	60	40	150
Bil-D	Diazo	35	25	0	n/a	n/a	25	35
Bil-T	Diazonium ion	300	50	0	n/a	n/a	50	300
Cholesterol	CHOD-PAP	2000	700	14	16	14	700	2000
Calcium	Schwarzenbach,o-cresolphthalein	2000	1000	60	60	60	1000	2000
CK	UV-NAC activated	1000	200	60	60	60	200	1000
CKMB	Immunological,UV	200	10	20	40	20	10	200
Creatinine	Creatinine Jaffe	800	1000	5	5	10	1000	800
GGT	γ-glutamyl-carboxy nitroanilide	1500	200	20	50	20	200	1500

Glucose	Hexocinase	1000	1000	60	60	60	1000	1000
HDLChol	Direct, non-immunologic	1800	1200	30	30	60	1200	1800
Iron	FerroZine ,without deproteinization	1500	200	60	60	60	200	1500
LDH	Lactate-pyruvate, UV)	900	15	60	60	60	15	900
Phosphorus	Molybdate,UV	1250	300	40	40	60	300	1250
Total Protein	Biuret	2000	1000	20	20	20	1000	2000
Triglyceride	GPO-PAP	0	700	10	10	35	700	n/a
Uric Acid	Uricase, PAP	1500	1000	40	40	40	1000	1500
UIBC	Direct,FerroZine	300	40	60	60	60	40	300
Ure	Urease,UV	1000	1000	60	60	60	1000	1000

Table 2. Distribution of affected tests according to hemolysis index (I.H) value

Hemolysis Index (I.H) Value	Affected Tests
11-15	CK-MB
16-24	CK-MB, D.BIL
26-40	CK-MB, D.BIL, LDH
41-49	CK-MB, D.BIL, LDH, AST, UIBC
52-181	CK-MB, D.BIL, LDH, AST, UIBC, T.BIL

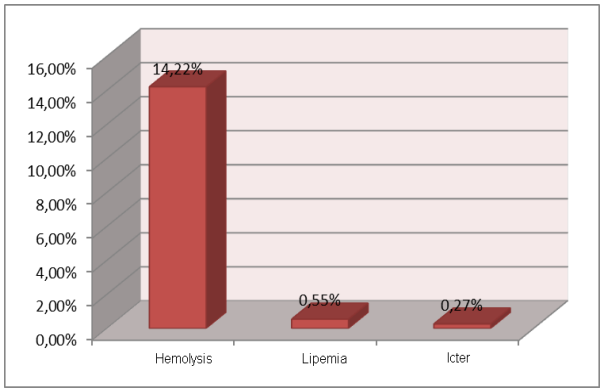

Figure 1. The percentage of interferences in all samples

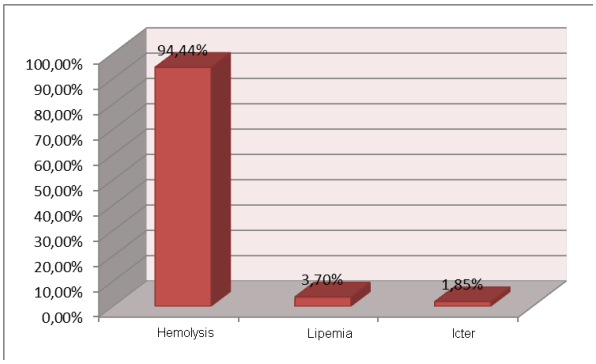

Figure 2. The percentage of interferences in samples that detected interferences

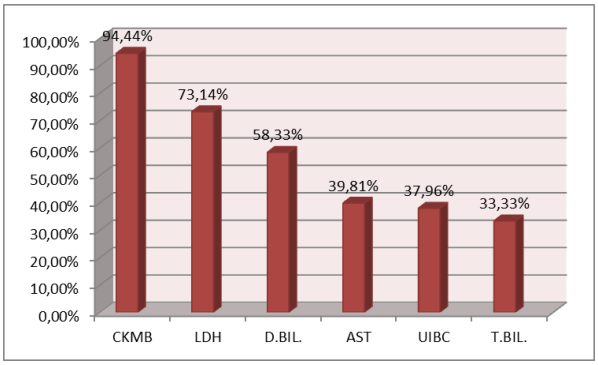

Figure 3. The percentage distribution of affected tests in interfering samples

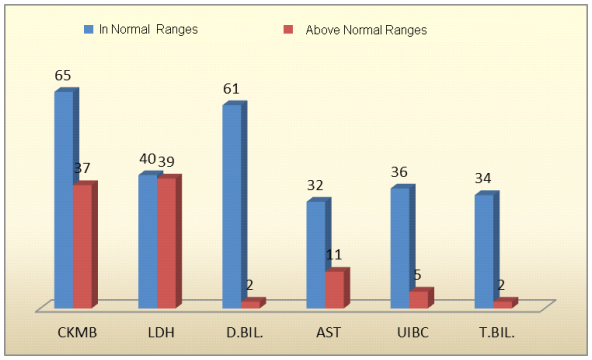

Figure 4: Quantitative comparisons of affected test results according to normal reference ranges or above.

Lipemia interferences were observed only in four samples. In these samples, we observed that only direct bilirubine was affected by lipemia while there were no effects on the other tests. Values of direct bilirubin affected by lipemia were within normal reference ranges in the four samples. Lipemia index (I.L.) values were lowest 38 and highest 55. Icter interferences were observed only two samples. In one of the samples, affected test parameters were cholesterol, CK-MB, creatinine, GGT, total protein and triglyceride, and icter index (I.I.) value was 22.

While total protein and creatinine were below normal reference ranges, the others were above normal reference ranges. In the other sample, affected tests were creatinine and triglyceride and I.I. value was 12. Creatinine was below normal reference ranges while triglyceride was within normal reference ranges. Because the number of samples in which lipemia and icter interferences were observed was few, percentage distribution calculations could not be done.

Discussion

Kroll and Elin described interference as “the effect of a substance present in the sample that alters the correct value of the result” (9). Four major endogenous components that often affect many laboratory test results are hemoglobin, bilirubin, lipids and paraproteins. In routine laboratory diagnoses, the most

crucial cause of preanalytical errors is hemolysis. In our study, the most cause of interference was found as hemolysis (94.44%). According to data reported by clinical laboratories, hemolysis is responsible for 40-70% of unsuitable and rejected samples. It is seen five times more than the other causes of unsuitable samples such as inadequate sample, clotted sample and faulty sample etc. (10,11).

Classically, hemolysis is release of hemoglobin and the other intracellular components to extracellular area following cell membrane damage. Visible hemolysis is not recognized until serum or plasma is separated. When hemoglobin concentration exceeds 0.3 g/L, hemolysis is recognized visually and it gives rise to red colored serum or plasma. Hemolysis can occur in vivo or in vitro and it is an undesirable situation, because, it affects accuracy and reliability of laboratory tests (11,12). Recent studies have reported that hemolysis affects many laboratory tests such as potassium, sodium, calcium, magnesium, bilirubin, haptoglobin, total protein, üric acid, aldolaz, amylase, LDH, AST, ALT, phosphorus, ALP, acid phosphatase, GGT, folate and iron etc. (13-15). In our study, only 6 of 23 studied parameters were affected from hemolysis.

These parameters were CK-MB, LDH, AST, total bilirubin, direct bilirubin and unsaturated iron binding capacity; other parameters weren't affected by hemolysis. Parameters which were most affected by hemolysis were respectively CK-MB, LDH, direct bilirubin, AST, unsaturated iron binding capacity and total bilirubin. In an article by Köseoğlu et al. İt was reported that the most affected parameters from hemolysis were AST, ALT, bilirubin and potassium and these parameters were affected by hemolysis even in very low hemoglobin concentration (0.5 g/L). Lippi et al. reported that they observed clinically significant variations of AST, LDH, chloride, potassium, sodium values due to hemolysis which was not recognized visually (0.6 g/L) (16,17). In our study, we observed that the number and type of affected test parameters varied according to I.H. value (I.H. value is proportional to the hemoglobin concentration in patient's sera, for example; if I.H. value is 500, hemoglobin concentration is 500 mg/dL). According to our results, we observed that CK-MB and direct bilirubin were affected by hemolysis even in the lowest I.H. values (I.H. 11-16). Although CK-MB was affected by hemolysis even in very low hemoglobin concentrations, it was amazing that CK results of samples with the highest I.H. values (I.H. 181) were not affected by hemolysis. Adenylate kinase which is released to extracellular area from intracellular area due to erythrocyte membrane damage causes a rise of CK and CK-MB levels through analytical interference. In order to minimize this interaction, adenylate kinase inhibitors such as adenosine monophosphate and diadenosine pentaphosphate are added into reactive mixture. For this purpose, Roche firm adds adenosine monophosphate and diadenosine pentaphosphate to their CK and CK-MB reactives. This implementation causes 97% inhibition for adenylate kinase activity and residual small amount of adenylate kinase activity does not affect total CK activity but very small amount of adenylate kinase activity can affect to CK-MB measurement. This information in prospectus of manufacturer was quite compatible with our results (18). We observed that LDH measurements were affected by I.H. from 26, AST and UIBC measurements were affected by I.H. from 41 and total bilirubin measurements were affected by I.H from 52. In the literature, information about the effect of hemolysis on tests is similar; however, there are different assessments about the interference degree of analysis by hemoglobin concentrations. Yiğitbaşı et al. reported that the effect of interference caused by hemolysis increased parallel to the degree of hemolysis and added that test results were gradually higher or lower. They reported that particularly, AST, ALT, direct bilirubin, sodium and potassium tests were affected even by very low hemoglobin concentrations. Yücel at al. reported that acid phosphatase, potassium and LDH were significantly affected by hemolysis. Ji at al. also evaluated serum interferences on Roche Cobas 6000 system.In their study, the lowest I.H. value was 40 and the affected parameters were AST, LDH, direct

bilirubin and UIBC; their results were compatible with our results (19-21).

In our study, the number of samples affected by lipemia was 4 and the number of samples affected by icterus was only 2. Only direct bilirubin was affected from lipemia while cholesterol, CK-MB, creatinine, GGT, total protein and triglyceride were affected from icterus. Whereas total protein and creatinine were negatively affected, the others were positively affected. The most common causes of lipemia are diet, alcohol intake, DM, hypertriglyceridemia, chronic renal failure, hypothyroidism, pancreatite, multiple myeloma, primary biliary cirrosis, lupus erithomatasus, estrogen intake. Lipemia interference occurs due to 3 different mechanisms: light scattering, increased nonaqueous phase, partition effect between polar and nonpolar phases. Increased bilirubin concentration causes chemical and spectral interferences (22, 23).

As a result, in order to prevent reporting of erroneous results, each sample should be evaluated against interference probability so that interference errors could be decreased and thus quality and patient safety could be improved. Hinckley et al. reported that visual evaluation was unsuccessful in erroneous sample detection (24). Glick et al. found that visual evaluation of hemolysis, lipemia, icterus were very little compatible with real concentration of interferent (25). Simundic et al. compared visual evaluation with automated spectrophotometric evaluation. They reported that visual evaluation was not reliable and suggested that automated systems which report serum indices should replace visual evaluation (26).

Use of serum indices should be expanded so that hemolysis and the other interferents are detected more reliably and faster, possibility of error is reduced, quality of laboratory diagnosis is increased, economical advantage is provided and patient security is not endangered. Serum indices can be seen as a fast and cheap way to facilitate and accelerate the laboratory processes for detection of icteric, lipemic and hemolytic samples. Quality of reported results is increased by serum indices because 100% of samples are controlled. As a result, serum indices will provide a reliable basis for detection of error due to interferent and thus for rejection of sample (27,28).

Conclusion

The samples received by the laboratory may be significantly influenced by interferences. The chance of identifying a possible visible interferent is greatly decreased when primary tubes are covered with several labels which prevent the clear inspection of the sample. A serum index result generated with the sample result ensures that all samples are correctly identified. Particularly, results of serum indices on the basis of parameters are much useful for monitoring of degree of interference. After analysis, while test results are obtained, at the same time, quality of samples is also automatically monitored. The improved clinical usefulness of the results allows better clinical decisions and better patient care.

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