Physiology & Biochemistry

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Review

Preanalytical variables and factors that interfere with the biochemical parameters: a review

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Abstract

Introduction

The total testing process, which begins with the order of the physician, includes the preanalytical, analytical and postanalytical phases and ends with the results ready for interpretation. To obtain a reliable test result requires detection of all steps however, to control the preanalytical stage is such a complex way that much of the steps are human dependent and out of the laboratory's control thus occupies the most erroneous part of the total testing. The worst side is that the error in that stage often becomes apparent in the analytical or postanalytical phase.

The aim is to highlight the multifactorial human dependent erroneous stage that affects the biochemical routine test results, which can be easily prevented with awareness and laboratory staff education. We will concentrate on the preanalytical errors which include specimen type selection, blood collection, blood collection equipments and the factors interfering with biochemical tests.

Conclusion

The quality of the analytical phase increased due to the interest, tight control and following the quality procedures both internal and external established by the medical laboratories and manufacturers.

Introduction

The total testing process includes the preanalytical, analytical and postanalytical phases which begins with the order of the physician and ends with the result ready for interpretation. With the improvements in the analytical phase by focusing on the analytical quality, the error magnitude decreased, thus the preanalytical stage constituted the most error-prone part with a percentage of 46–71[1,2].

The preanalytical stage is so complex that a mistake at any step often becomes apparent in the analytical or postanalytical phase. The error magnitude increases especially in the human dependent parts, e.g. sample collection, handling, transportation, storage which are mostly out of the laboratory's control. With the increasing number in laboratory tests per patients, the burden of phlebotomy increased[3].

In this review we will concentrate on the preventable preanalytical errors which include specimen type selection, blood collection, blood collection equipments and the factors interfering biochemical tests. Better control of these variables will improve the total analysis quality for which the big role in the play is given to the laboratories by the accreditation agencies[4,5].

Blood collection errors

Because blood exerts the physiological states of the body systems, much emphasis has been placed on analysing blood samples.

- Venipuncture: intravenous access for blood collection, also named as phlebotomy, is commonly performed from the median cubital vein. A good phlebotomy technique performed has to minimise trauma to the patient, reduce the risk of recollection and minimise the risk of haemolysis. The phlebotomy errors are detected to cause 24%–30% of a serious patient misdiagnosis[4].
- During blood collection, the arm has to be positioned downward to avoid possible backflow of additives (EDTA, heparin, etc.) because of the vacuum inside the tube. The phlebotomy site with a running IV has to be avoided, however if there is no alternative for exp. because of mastectomy, hematoma, or infection, the distal site of the IV has to be preferred.
- Cleaning the venipuncture site: the site for venipuncture is to be cleaned with 70% ethanol. Attention is needed for ethanol to be dried before the needle is inserted into the vein otherwise alcohol causes erythrocyte membrane rupture and subsequent haemolysis thus the interferences. Samples for blood culture should be collected after cleaning the selected site with povidone–iodine.
- Tourniquet application: the tourniquet should be released once the first blood flow was established. More than 1 min of tourniquet left results in haemoconcentration occurrence and test errors[6]. Haemoconcentration causes increases in serum calcium and potassium[7]. Clenching fist causes elevation in serum CK and potassium.
- Needle or syringe: syringe usage in venipuncture is a major cause of in vitro haemolysis due to the force applied during aspiration and transfer into the tube. The vacuum inside the tube is predetermined to collect appropriate volume of blood into tubes. However, performing venipuncture with a syringe and further aliquoting the blood from syringe often result with a small volume of blood in the tube when multiple types of specimens are needed.

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- The needle with a large diameter (low-gauge) or small gauge can cause cell damage. Mostly preferred needle size is 21-gauge (green).
- Centrifugation of the small volume of blood is another cause of haemolysis. Underfilling the evacuated tubes caused a significant decline in bicarbonate measurements due to pseudometabolic acidosis[8].
- Order of drawing tubes: the blood collected in a specific order avoids cross contamination of additives between tubes because of the needle piercing the top of the tube and getting into contact with the additive inside (Table 1). Examples of the common carryover problems observed are the EDTA caused interference which is easily determined by marked hyperkalemia, hypocalcemia (lower than 0.5 mmol/L), hypomagnesemia and hypozincanemia. The other common interference is the carryover of clot activators into the sodium citrate tubes[9]. The list of the order of blood draw recommended by CLSI – Clinical and Laboratory Standards Institute (formerly NCCLS)[10].

Proper mixing the tube after collection for five times is recommended by the tube manufacturers.

Specimen type

Blood is an important biological material that exerts the physiological states of the body functions. Three types of blood specimens: whole blood, plasma and serum can be used and selected according to the needs of the laboratory and the analyte to be studied. Most routine clinical chemistry and immunochemistry assays are suitable for analysis with either serum or plasma. However there are some precautions with the use of anticoagulated plasma specimen which produces differences for some analytes compared with serum.

Whole blood sample

Whole blood sample can be obtained easily by both collecting blood in a tube with a type of anticoagulant and skin puncture. The advantage of the use of whole blood is the elimination of the sample preparation period for urgent results. The first drop of blood obtained by skin puncture should be discarded of its high content of tissue fluid which increases with the squeezing of the fingertip. Capillary samples are more similar to arterial blood values than venous blood values. Venous blood glucose concentrations are approx. 7% lower than capillary samples. The difference among arterial, capillary, and venous samples is low in fasting subjects.

Whole blood sample is needed to be mixed prior to use. Freezing whole blood is not recommended, or when the tube stand is in the refrigerator, sample is ready for the analysis when the tube is warmed up enough to room temperature since platelets do not tolerate refrigeration which causes cell modification[11].

Table 1 Order of blood draw
1. Sterile-blood culture (yellow top or bottles)
2. Coagulation (light blue)
3. Non-additive (red top)
4. Gel separator tube (red or gold)
5. Heparin tube (green top)
6. EDTA (lavender/purple top)
7. Oxalate/fluoride (grey top)
8. All other tubes

Plasma

Plasma samples are mostly the preferred type in the emergency department because of its small turn around time. With centrifugation of the whole blood, we obtain plasma which contains fibrinogen and the anticoagulant different from serum. The hazy colour of the plasma comes from the fibrinogen inside. The cloudy coloured thin layer between the liquid form (called plasma) and RBC is named as "buffy coat" which consists of a mixture of WBCs and platelets (Figure 1). For small volumes of blood, or for hardly collected samples, plasma is to be the preferred type because fibrin clots retain some water, and the remained liquid portion decreases. Owing to the higher volume of the watery portion of the blood than serum, the concentrations are lower in plasma. Because plasma contains fibrinogen different from serum, total plasma protein concentration is approx. 3% higher than serum[12] (Figure 2).

Serum

Serum is the watery portion of blood that remains after coagulation and is free from fibrin (Table 2). Serum can be obtained by centrifugation of the blood collected into the tube without an anticoagulant. Because the platelets and coagulation factors are activated when blood vessels are punctured, their activation continues in sample tubes, platelets release a small amount of potassium into the serum during the clotting process[7], therefore the lysis of blood cells (especially the platelets) causes an increase in the concentrations of the platelet components such as potassium[14], Neuron Specific Enolase and acid phosphatase[15].

Blood collection tube interference

The manufacturers coated the stoppers with lubricant to ease the removal and to maintain the lower pressure inside the tubes[16]. It is

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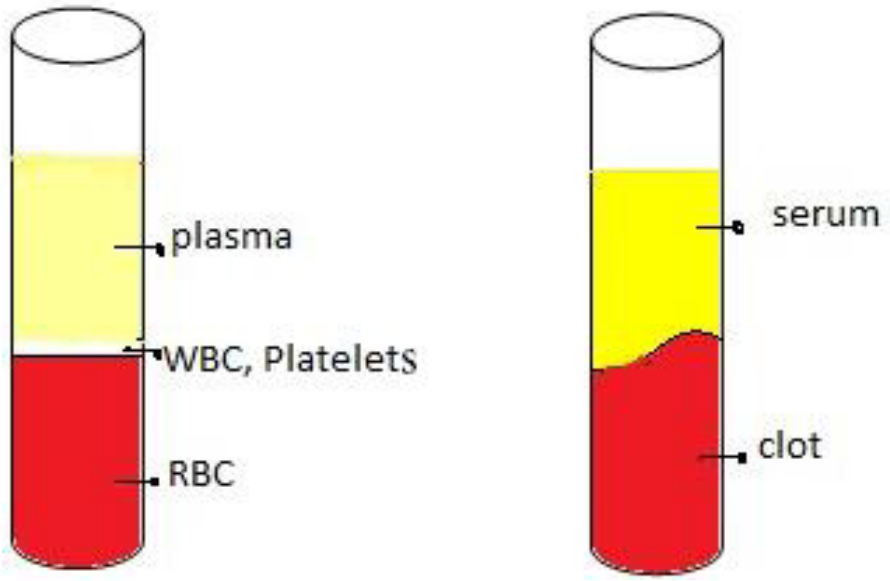

Figure 1: Plasma and serum.

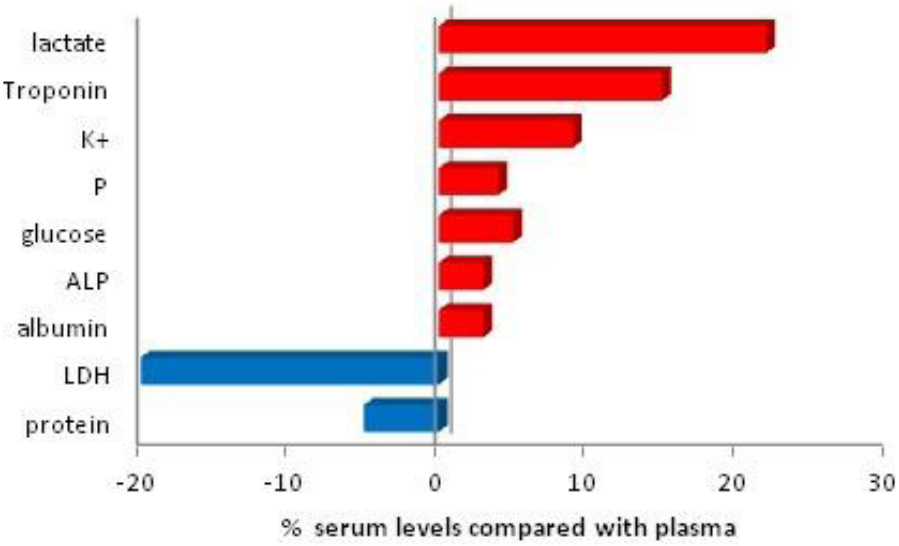

Figure 2: Analyte concentrations in serum versus plasma (%).

Table 2 Awareness required for selecting plasma instead of serum
1. The effect of anticoagulant
2. Stability of the analyte
3. Dilutional effect of the liquid anticoagulant
4. The interferent effect of proteins and lipoproteins[13]

possible that the components of the stopper and the lubricants may contaminate blood samples. Silicone in the stopper lubricant caused interference in the magnesium assay[17].

For a rapid and complete separation of serum from the clot, the "silicone-separator gel" (SST) tubes were introduced, which also contain silica particles to facilitate clotting. Gel formulations are comprised of a block copolymer, a gelling agent and a liquid vehicle. During centrifugation, the gel moves upwards physically to the supernatant–cell interface because of its intermediate density (1.04 g/cm^3) to that of the serum[18]. The mostly preferred gel material is a thixotropic polyester gel which is substantially hydrophobic. However, storing samples for hydrophobic drug assay caused interferences[19]. Chang et al.[20] observed falsely increased CRP concentrations in serum separator tubes. Storing or freezing the samples on the gel is not recommended for measuring homocysteine assessment[21]. Another problem which may be encountered with the use of gel materials in the evacuated blood collection tubes is the separation of the silicone oil or other gel materials during storage of collection tube. Those separated materials are lighter in density than the separator gel, so they rise on the top surface of the serum sample. This may disable the probe of the autoanalyser by coating the distal end of the electrical probe member, and the probe will enter the gel material erroneously. Separator gels may cause higher values for ionised calcium because of the liberation of calcium from the gel contents, and liberation of acid causes a lower pH[22,23].

The term "gel flotation" is a kind of inappropriate gel formation especially with samples that have higher densities than gel material. As an example contrast media caused gel floating was observed[24]. In patients with multiple myeloma, the inappropriate gel location was shown because the high protein content caused high specimen density and resulted in inappropriate gel formation[18].

The recentrifugation of the specimens stored in the separator gel tube causes pseudohyperkalemia[25]. This interference originates from the serum remaining in the clot, which now contains a much higher

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concentration of potassium, is added to the original serum sitting above the thixotropic gel.

Additive caused interference

Lithium heparin, ammonium heparin or sodium heparin are the anticoagulants which are not appropriate to use for lithium, ammonium and sodium determinations, consequently. The thrombin evacuated blood collection tubes contain thrombin as a clot activator. However, shortening the coagulation time causes some interferences detected for chloride (Cl), calcium, LDH and potassium (K^+)[26]. The higher values for Cl are attributed to the rapid separation from the cells, which prevents uptake of Cl by the erythrocytes. The increase in LDH and K^+ may be due to invisible haemolysis, and high calcium values may be due to the rapidity of the clotting process.

EDTA is unsuitable for iron and calcium analysis as it chelates both iron and calcium and has an effect to inhibit alkaline phosphatase (ALP), creatine kinase (CK) and leusin aminopeptidase activities, probably by chelation of metallic cofactors. Heparin is unsuitable for the CK assay[14].

Factors affecting biochemical test results

Glucose

Tight control of blood glucose levels requires the same sample type besides the same analysis method because a difference (<4%) in two common assay methods (hexokinase and glucose oxidase method) has been determined. Serum glucose concentrations were found to be 2%–5% higher than plasma as a result of fluid shift from erythrocytes to plasma because of anticoagulants[27,28]. Plasma glucose has been determined as 10%–15% higher than whole blood, because a major component of the measured glucose is located outside the erythrocytes[28]; therefore the whole blood glucose is dependent on the value of hematocrit[29]. With the decrease in hematocrit, whole blood glucose increases.

- Glucose concentrations: whole blood < plasma < serum.

The storage of sample tubes for glucose analysis is problematic. The concentration decreases due to the continuing glycolytic action of erythrocytes and leukocytes[30,31] cited by Tietz[32]. The rate of decrease in plain tubes is sensitive to the clot contact time and temperature. Because glycolysis occurs in the cellular part of the blood, complete barrier formation of the gel separator tube and storage in the refrigerator protects glucose concentrations (−2.1%, clinically insignificant) for up to 36 h of storage[33]. To ease the effect of glycolysis, NaF addition into the tube for its inhibitory effect on enolase, an enzyme in the glycolytic pathway, has been recommended, however, during the first 1–2 h the effect was found as inadequate[34].

Potassium

Pseudohyperkalemia is defined as a marked elevation of potassium in the absence of clinical pathology in electrolyte balance. In serum, the cause might be due to leakage of potassium from platelets during the clotting process, or white cell breakdown or erythrocyte damage. Breakdown of RBCs and release of haemoglobin and other intracellular components into the plasma is called haemolysis and the colour changes to rose or even red. Haemolysis caused sample rejection rate is high (60%) for which the worst part is the interference detected even in invisible haemolysis[35,36].

Pseudohyperkalemia may result from leukocyte lysis during phlebotomy and during whole blood coagulation in patients with malignant leucocytosis and platelet lysis in myeloproliferative disorders[37,38].

Lower potassium concentration in plasma is attributed to the prevention of clot formation with platelet rupture and potassium release.

Bilirubin

Haemolysis interferes in the bilirubin procedure with pseudo-peroxidase activity of free haemoglobin by inhibiting the diazonium colour formation. Due to the haemolysis, total bilirubin concentrations were found as decreased even at mildly haemolysed specimens (0.5–1 g/L)[35].

Because bilirubin is photosensitive, samples have to be protected from the light exposure up to analysis.

AST (aspartate aminotransferase)

In haemolysed specimens, AST rich cell content enters into the plasma, increasing the AST level falsely.

LDH (lactate dehydrogenase)

LDH activity is present in all cells, in the cytoplasm, thus the lysis of cells causes falsely elevated LDH levels. The 0.27 g/L of free Hb in plasma resulted in an increase in levels of more than 20% which is at a degree of an invisible haemolysis[35].

Creatinine

High bilirubin concentrations may interfere with the Jaffe method, a colourimetric method for creatinine assessment, where the assay absorbance is near the bilirubin absorbance peak of ~456 nm[39]. Jaffe assay system is very alkaline and bilirubin is oxidised to biliverdin during the assay period and causes a decrease in absorbance which is proportional to the bilirubin concentration.

Jaffe reaction can be influenced also by lipemia and/or haemolysis which increases serum creatinine falsely[40].

Haemolysed samples that contain foetal haemoglobin (HbF) interfere with the Jaffe reaction, and it is possible to obtain negative creatinine results. Because HbF is alkali resistant, colour change occurs slowly in the presence of NaOH and interferes in the reaction, therefore in babies <1 years of age, enzymatic method is recommended[41].

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Protein

As mentioned above, high protein concentrations in serum or plasma causes a misappropriate gel formation in serum separator tubes[18].

The presence of IgM class paraproteins interferes in the determination of total serum protein with the Biuret method[42].

Sodium

Pseudohyponatraemia may result from the sample collection from IV site, thus the sample is diluted by the hypotonic fluid (5% dextrose), the sodium levels will result as hyponatraemia which can easily be identified by the high serum glucose level[43]. Increased viscosity due to the monoclonal gammopathy and subsequent decreased watery portion of plasma can thus cause false low sodium concentrations[43].

Discussion

The author has referenced some of her own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed.

The error magnitude in the total testing process depends on the patient population studied (inpatient, outpatient, paediatric, etc.) and to the capacity of a system of error reporting and identification. Therefore, studies reveal different error rates about, however there is a consensus that the preanalytical phase constitutes the big portion[2,44] (Figure 3). It is also noted that, the pre- and postanalytical errors were defined as human dependent and preventable, for which the rate was recorded as 73.1%[44]. The most frequent problem in the preanalytical phase arises from the mistakes in the tube filling, inadequate anticoagulant-blood ratio which was followed by patient misidentification[44]. Moreover the negative impact of preventable laboratory errors on patient outcomes was observed in 24.4% of cases, in which most of these errors have resulted in test repetition.

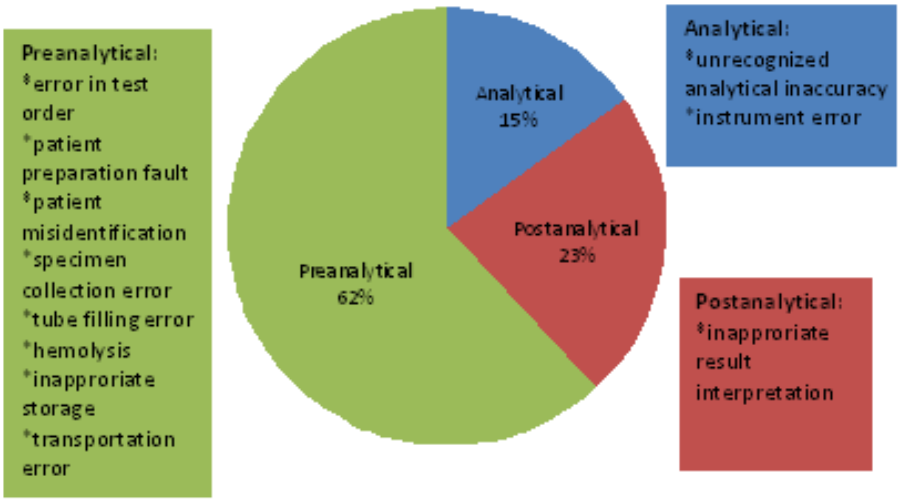

Figure 3: Error rates in the total testing process.

With the increasing variability and interest in diagnostic laboratory tests, the number of laboratory tests per patient increased over the years. Consequently, the length of hospital stay and costs were increased, however no significant decrease in mortality was determined[3]. Above all, during hospitalisation, haemoglobin levels showed a decreasing trend, to make matters worse some patients needed a blood transfusion because of the impact of phlebotomy[3]. Accordingly, Chant et al.[45] suggested that even small decreases in the phlebotomy volume reduced the number of transfusions required.

Unfortunately, erroneous values resulted in a range of reference intervals that can mask the actual result[46]. As an example, invisible haemolysis can mask hypokalaemia thus may cause misdiagnosis and not many laboratories use analysers that detect serum indices; therefore haemolysis is still a continuing challenge for laboratories[35,47]. In this context, for unexpected test results, communication with physician is important and the test has to be repeated after obtaining meaningful information on the quality of sample collection, but if an unsuitable sample is detected, a new sample has to be requested.

Conclusion

The quality of the analytical phase increased due to the interest, tight control and following the quality procedures both internally and externally established by the medical laboratories and manufacturers. The same interest for the preanalytical errors will also decrease the errors though seems like a puzzle, but possible.

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