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REPORT

On Medical Testing of Medical-Purpose Item

"AMP Noninvasive Hemogram Analyzer
as per Specification ТУ У 33.1-22716816-001:2006"
UKTZED Code: 9018 19 90 00

Manufactured by Research and Production Complex "Biopromin" Ltd (Ukraine)

Tested Under Assignment of State Service for Medical Products and Medical-Purpose Items
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ABSTRACT

This paper provides materials on clinical study of medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10, manufactured by research and production complex "Biopromin" Ltd (Ukraine), designed to provide patient's clinical blood analysis data (number of erythrocytes, number of hemoglobin; number of leucocytes; leukogram analysis – number of stab neutrophils, number of segmented neutrophils, number of eosinophils, lymphocytes, monocytes; erythrocyte sedimentation rate) without invasive blood sample drawing with subsequent data processing using the "USPIH" software.

Clinical research of healthy volunteers was carried out by comparative analysis with the data provided by the certified "Sysmex N-2000" hematology analyzer (Japan). The red blood was analyzed by the number of erythrocytes and hemoglobin, the white blood was analyzed by the number of leucocytes and lymphocytes. The measurement results were processed with the use of statistical methods and metrological control methods.

The research allowed to determine that the medical-purpose item under test ensures the required reproducibility at 95 percent confidence level but the statistical characteristics have a critical value. Parallel testing by standard (conventional) laboratory methods is advisable.

The report contains 18 pages, 4 tables.

Bibliography: 10 sources.

Key words: clinical blood analysis, leukogram, hematology analyzer.

INTRODUCTION

At the beginning of 1990's, the World Health Organization (WHO) determined the strategy of public health care development in the whole world by three words: "Focus on patient". In the light of this strategy, one of the main objectives of professional activity of a doctor or a pharmacist is optimization of diagnostic and therapeutic measures for preventive health care, identification and treatment of a disease, and increase of efficiency and safety of treatment of a particular patient.

Illness diagnostics is always carried out with the use of objective methods of patient examination and, first of all, blood analysis. In some cases changes in qualitative and quantitative composition of peripheral blood (blood corpuscles) allow to identify inflammatory and allergic processes, blood-forming system disease, and contribute to subsequent comprehensive patient examination and identification of a disease that has not yet declared itself.

Blood analysis plays a leading role among various comprehensive diagnostic methods. Correct and early recognition of a disease, reasonable treatment, true forecast of disease course are often impossible without morphological and biochemical blood analysis data. Blood picture is often a more sensitive diagnosis factor reflecting the condition of an organism unlike traditional clinical analysis methods. Blood analysis allows to detect discrepancies even with those patients and at those stages of disease when no clinical presentations are available and the results of other examinations are within the physical standard limits. Blood picture study in the course of disease is of special importance because it allows to judge of the severity of process, patient status improvements or degradations.

Clinical blood analysis is of exceptional importance. Comprehensive clinical blood analysis is a basic examination to determine the number of hemoglobin, number and morphology of erythrocytes, globular value, number and composition of leucocytes and erythrocyte sedimentation rate.

Leukogram analysis is widely used in practical medicine as an important additional method of clinical study of patient's condition for diagnostics of blood system diseases and many other diseases. Leukogram is one of the most frequently used and most important laboratory examinations and is required as a supplement to determine the absolute number of leucocytes. Determination of the number of leucocytes presents a complete clinical value only when correlated to the data obtained after differential determination of leucocytes.

AMP Noninvasive Hemogram Analyzer manufactured by research and production complex "Biopromin" Ltd is an instrument that allows to apply sensors to the “reference” biologically active points on a human body surface and measure temperature therein to determine the indicators of a comprehensive blood analysis which are used for diagnostics of diseases in medial practice.

RESEARCH OBJECTIVE

The objective of clinical research is to test the capability of medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine) to automatically determine the indicators of a clinical blood analysis apply resulting from the measurement of temperature in “reference” points on a human body without taking blood samples and damaging the skin integument, to evaluate the instrument safety and to determine unforeseen side effects during its operation.

RESEARCH TASKS

Use the base of the clinicodiagnostic center of the National University of Pharmacy and healthy volunteers:

- to perform clinical examination of indicators of peripheral blood using the medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine);
- to perform comparative analysis of the peripheral blood indicators examination results using a certified "Sysmex N-2000" hematology analyzer (Japan);
- to perform comparative metrological analysis of the examination results with the use of statistical processing methods;
- to perform evaluation of operational safety of the medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine) basing on subjective feelings of the volunteers.

RESEARCH MATERIALS AND METHODS

Specially designed microprocessor sensors of the medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine) were applied to certain “reference” biologically active points on a human body surface (after pre-treatment of skin and sensors by 70 % ethyl alcohol for degreasing):

- blue sensor - to the bifurcation of the left carotid artery in the area of annular cartilage;
- green sensor - to the bifurcation of the right carotid artery in the area of annular cartilage;

- yellow sensor - to the left axillary crease (by the principle of a thermometer);
- violet sensor - to the right axillary crease (by the principle of a thermometer);
- red sensor - to the abdominal area (inside the umbilical crease. If the umbilicus is absent - to the area where it used to be before surgery).

The measurement procedure, depending on the rate of human body temperature stabilization, took from 180 to 720 seconds.

In the process of testing of the medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine), the following was determined:

- number of erythrocytes, $\times 10^{12}$/l and number of hemoglobin, g/l, as the indicators of red blood condition;
- number of leucocytes, $\times 10^{9}$/l, as the indicator of white blood condition;
- number of lymphocytes, %, as the indicator of leukogram.

The results were analyzed by comparing them with the same indicators of the venous blood obtained with the use of a certified hematology analyzer (CHA) in a certified laboratory.

Venous blood for examination with the use of a certified hematology analyzer was taken by venepuncture of median cubital vein in test tubes Venosafe VF-053 SDK with EDTA. The composition of peripheral blood was determined using the “SYSMEX” N-2000 instrument (Japan) according to its operating manual. The results of examination were presented the next day after measurement using the Noninvasive Hemogram Analyzer and blood drawing.

The following criteria were used as the basis to accept the volunteers for examination:

1. Absence of inflammatory, anemic, allergic, oncological diseases.
2. Willingness of the volunteer to take part in the research.

The following criteria were used as the basis to decline participation of the volunteers in the examination:

1. Inflammatory, anemic, allergic, oncological diseases.
2. Treatment by medicines that can influence the hemogram.
3. Unwillingness of the volunteer to take part in the research.

PATIENT EXAMINATION CHART

Functional Condition Indicators

Indicators Under Examination	Before Measurement	After Measurement
Arterial pressure, mm Hg		
Cardiac rate, beats per minute		
Respiratory rate, per minute		

Laboratory Examination Data

Blood Indicators	Determination Method	
	Certified Hematology Analyzer (Venous blood)	AMP Noninvasive Hemogram Analyzer
Erythrocytes, $\times 10^{12}$/l		
Hemoglobin, g/l		
Leucocytes, $\times 10^{9}$/l		
Lymphocytes, %		

Registration of Adverse Symptoms

Date	Side Effect	Degree of Manifestation	Arresting Measures

The obtained results were statistically processed according to the following standards:

- ДСТУ 3514-97. Statistical Methods of Control and Regulation. Terms and Definitions. - Kyiv: Derzhstandart of Ukraine, 1997. - 52 pages.
- ГОСТ ИСО 5725-1-2003 Accuracy (Correctness and Precision) of Methods and Results of Measurements. Part 1. General Information and Definitions.
- 1.8.31. ГОСТ ИСО 5725-2-2003 Accuracy (Correctness and Precision) of Methods and Results of Measurements. Part 2. Main Method to Determine Repeatability and Reproducibility of Standard Measurement Method.
- 1.8.32. ГОСТ ИСО 5725-3-2003 Accuracy (Correctness and Precision) of Methods and Results of Measurements. Part 3. Intermediate Indicators of Precision of Standard Measurement Method.
- 1.8.33. ГОСТ ИСО 5725-4-2003 Accuracy (Correctness and Precision) of Methods and Results of Measurements. Part 3. Main Methods to Determine Correctness of Standard Measurement Method.
- 1.8.34. ГОСТ ИСО 5725-5-2003 Accuracy (Correctness and Precision) of Methods and Results of Measurements. Part 5. Alternate Methods to Determine Precision of Standard Measurement Method.

- 1.8.35. ГОСТ *И*СО 5725-6-2003 Accuracy (Correctness and Precision) of Methods and Results of Measurements. Part 6. Use of Accuracy Values in Practice.

Sample group measurements were taken in terms of 30 measurements for each hematology indicator for two groups: men and women. Measurements taken with the use of a standard hematology analyzer were considered as standard technique, satisfactorily accurate, certified and accepted by representative of the World Health Organization (hereinafter referred to as the standard method). Measurements taken with the use of the medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine) are hereinafter referred to as the new method. The measurement results were processed individually for two groups. Each blood indicator was determined individually: 4 parameters for men and 4 parameters for women. Total number is 8 indicators.

Plan of statistical processing of the results:

1) Determination of mean value for each indicator and root-mean-square deviation.
2) Calculation of coefficient of correlation between the values of each hematology parameter measured by the standard method and by the new method. Determination of statistical significance of the coefficient of correlation: formulation of a hypothesis about the independence of results of parameter measurement by the standard method and by the new method (H_0: $\rho = 0$) and verification of such hypothesis. If it was accepted, the results were considered to be independent from each other and the correlation between them was regarded as statistically insignificant. If the hypothesis deviated, the measurement results were considered to be dependent upon each other and the correlation between them was regarded as statistically significant.
3) Interval estimate for each hematology parameter and determination of overlap percentage of parameter intervals measured by the standard method and by the new method.
4) Formulation of a hypothesis about equal precision of the standard method and the new method (H_0). The standard method was considered as satisfactory and the respective results were considered to be recognized in medial practice. i. e. master reference for the new method. Based on this analysis, a decision was made as to correspondence of the new method to the requirements of medical practice.

5) Accomplishment of the above analysis for the combined sample group (men and women together) of the measured leucocytes. The sample group comprised 60 measurements.

RESEARCH RESULTS

Tables 1 and 2 contain anthropometric and physiological characteristics of the volunteers and the results of their examination - values of peripheral blood indicators obtained by various methods.

Table 1

Anthropometric and Physiological Characteristics of Volunteers

	Number of Persons	Age, Years	Body Weight, kg	Cardiac Rate, Beats per Minute
Men	30	29.77±2.37	79.57±2.40	73.23±1.10
Women	30	21.93±0.66	59.40±1.85	78.20±0.95
TOTAL:	60	25.85±1.32	69.48±1.99	75.72±0.79

The research engaged 60 persons: 30 men and 30 women of normosthenic type aged from 17 to 63. The average age of the volunteers was 25.85±1.32 years, the average body weight was 69.48±1.99 kg, the average cardiac rate was 75.72±0.79 beats per minute. Respiratory rate and arterial pressure were within physiological norms.

The results were statistically processed to make an objective comparative evaluation of the new method of determination of blood indicators and the traditional method used in medical practice (Tables 3 and 4).

Table 3

Results of Statistical Processing of Red Blood Indicators Depending on Volunteer Sex

Indicators	**Men**		**Women**	
	AMP (n=30)	**CHA (n=30)**	**AMP (n=30)**	**CHA (n=30)**
ERYTHROCYTES, $\times 10^{12}$/l				
average value rms deviation conf. interval	4.74 0.29 4.63÷4.85	4.78 0.31 4.67÷4.90	4.28 0.32 4.16÷4.40	4.10 0.31 4.00÷4.23
Hypothesis about equality of dispersions, at significance level α=0.05 ($F_{0.975}$)				
Z_{cr} Z_m	2.61 1.10 $Z_m<Z_{cr}$ accepted		2.61 1.01 $Z_m<Z_{cr}$ accepted	
Determination of statistical values:				
Z_{cr} Z_m	2.042 0.548 $Z_m<Z_{cr}$ accepted		2.042 2.022 $Z_m<Z_{cr}$ accepted	
Hypothesis about equal accuracy of the standard and the new methods in measuring the number of erythrocytes - *accepted*.				
HEMOGLOBIN, G/L				
average value rms deviation conf. interval	153.95 7.64 151.10÷156.80	158.47 9.41 154.96÷161.97	131.83 10.02 128.10÷135.56	133.97 11.26 129.77÷138.16
Hypothesis about equality of dispersions, at significance level α=0.05 ($F_{0.975}$)				
Z_{cr} Z_m	2.61 1.52 $Z_m<Z_{cr}$ accepted		2.61 1.26 $Z_m<Z_{cr}$ accepted	
Determination of statistical values:				
Z_{cr} Z_m	2.042 2.040 $Z_m<Z_{cr}$ accepted		2.042 0.777 $Z_m<Z_{cr}$ accepted	
Hypothesis about equal accuracy of the standard and the new methods in measuring the number of hemoglobin - *accepted*.				

Table 4

Results of Statistical Processing of White Blood of Volunteers

Indicators	AMP (n=60)	CHA (n=60)
LEUCOCYTES, $\times 10^9$/L		
average value rms deviation conf. interval	5.92 1.09 5.84÷6.73	6.29 1.75 5.64÷6.20
Z_{cr} Z_m	1.98 1.366 $Z_m<Z_{cr}$	
Hypothesis about equal accuracy of the standard and the new methods in measuring the number of leucocytes - *accepted*.		
LYMPHOCYTES, %		
average value rms deviation conf. interval	31.34 4.53 30.18÷32.49	32.35 7.87 30.34÷34.36
Z_{cr} Z_m	1.98 0.864 $Z_m<Z_{cr}$	
Hypothesis about equal accuracy of the standard and the new methods in measuring the number of lymphocytes - *accepted*.		

Red blood indicators - the number of erythrocytes and the level of hemoglobin were evaluated with respect to the volunteer sex.

Average number of erythrocytes in men, when measured by the standard method, was $4.74\pm0.29\times10^{12}$/l, and when measured by the new method - $4.78\pm0.31\times10^{12}$/l, meaning uncertain difference ($p>0.05$). When verifying hypothesis about equality of dispersions at significance level $\alpha=0.05$, the obtained statistical indicators (Z_m) allowed to make a conclusion - “Hypothesis about equal accuracy of the standard and the new methods in measuring the number of erythrocytes is accepted”. The level of hypothesis acceptance $Z_m(0.548)<Z_{cr}(2.042)$ is sufficient.

Average number of erythrocytes in women, when measured by the standard method, was $4.10\pm0.31\times10^{12}$/l, and when measured by the new method - $4.28\pm0.32\times10^{12}$/l, meaning uncertain difference ($p>0.05$). When verifying hypothesis about equality of dispersions at significance level $\alpha=0.05$, the obtained statistical indicators (Z_m) allowed to make a conclusion - “Hypothesis about equal accuracy of the standard and the new methods in measuring the number of erythrocytes is accepted”. However, the level of hypothesis acceptance $Z_m(2.022)<Z_{cr}(2.042)$ is critical (too close values).

Average number of hemoglobin in men, when measured by the standard method, was 158.47 ± 9.41 g/l, and when measured by the new method - 153.95 ± 7.64 g/l, meaning uncertain difference ($p>0.05$). When verifying hypothesis about equality of dispersions at significance level $\alpha=0.05$, the obtained statistical indicators (Z_m) allowed to make a

conclusion - “Hypothesis about equal accuracy of the standard and the new methods in measuring the number of hemoglobin is accepted”. However, the level of hypothesis acceptance $Z_m(2.040)<Z_{cr}(2.042)$ is critical (too close values).

Average number of hemoglobin in women, when measured by the standard method, was 133.97±11.26 g/l, and when measured by the new method - 131.83±10.02 g/l, meaning uncertain difference ($p>0.05$). When verifying hypothesis about equality of dispersions at significance level $\alpha=0.05$, the obtained statistical indicators (Z_m) allowed to make a conclusion - “Hypothesis about equal accuracy of the standard and the new methods in measuring the number of hemoglobin is accepted”. The level of hypothesis acceptance $Z_m(0.777)<Z_{cr}(2.042)$ is sufficient.

Condition of white blood of volunteers was evaluated by measuring the number of leucocytes and lymphocytes in mixed sample group - the number of measurements was 60.

Average number of leucocytes in volunteers, when measured by the standard method, was $6.29\pm1.75\times10^9$/l, and when measured by the new method - $5.92\pm1.09\times10^9$/l, meaning uncertain difference ($p>0.05$). When verifying hypothesis about equality of dispersions at significance level $\alpha=0.05$ and n=60, the obtained statistical indicators (Z_m) allowed to make a conclusion - “Hypothesis about equal accuracy of the standard and the new methods in measuring the number of leucocytes is accepted”. The level of hypothesis acceptance $Z_m(1.366)<Z_{cr}(1.98)$ is sufficient.

Average number of lymphocytes in volunteers, when measured by the standard method, was 32.35±7.87 %, and when measured by the new method - 31.34±4.53 %, meaning uncertain difference ($p>0.05$). When verifying hypothesis about equality of dispersions at significance level $\alpha=0.05$ and n=60, the obtained statistical indicators (Z_m) allowed to make a conclusion - “Hypothesis about equal accuracy of the standard and the new methods in measuring the number of lymphocytes is accepted”. The level of hypothesis acceptance $Z_m(0.864)<Z_{cr}(1.98)$ is sufficient.

Thus, during statistical processing of the results of measurement of blood indicators in healthy volunteers (number of erythrocytes, hemoglobin, leucocytes and lymphocytes)we accepted the hypothesis about equal accuracy of the standard hematology analyzer and the medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine).

However, taking into account the critical level of hypothesis acceptance during measurement of erythrocytes and hemoglobin, it is recommended to perform parallel verification of those indicators by standard (conventional) laboratory methods.

During the tests, no single occasion of adverse effect of the medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine) on the health of healthy volunteers was detected.

SUMMARY

1. Basing on the results of comparative examination of the medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine), it was demonstrated that the medical-purpose item under test ensures the required reproducibility of blood indicators (number of erythrocytes, hemoglobin, leucocytes, lymphocytes) at confidence level of 95 % during examination of healthy volunteers.

2. The test results demonstrated absence of adverse effect of the medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine) on the health of patients.

3. The designers of the medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine) should improve the configuration of measuring sensors to achieve a better contact with skin and to prevent thermal influence of the operator's and patient's hands.

4. Taking into account quite limited statistical sample group, threshold level of hypothesis acceptance when measuring erythrocytes and hemoglobin and the type of examination (examination of 60 healthy volunteers), the medical-purpose item "AMP Noninvasive Hemogram Analyzer as per Specification ТУ У 33.1-22716816-001:2006", UKTZED Code: 9018 19 90 10 manufactured by research and production complex "Biopromin" Ltd (Ukraine) is recommended for use in medical practice in Ukraine in parallel with conventional methods of blood analysis until statistical sample group reaches considerable level to enhance indications for use, namely: monitoring comprehensive blood analysis indicators in patients with secondary and primary disorders in the blood system.

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