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Evaluation of an electrochemical biosensor for uric acid measurement in human whole blood samples

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ABSTRACT

Background: Uric acid measurement has become increasingly important, and electrochemically modified detection method based portable devices hold a dominant position in the market for point of care and self-monitoring of uric acid blood levels. However, there has been a lack of detailed performance evaluation of the electrochemical detection devices that are currently being used in professional health care facilities and for home self-monitoring of uric acid.
Methods: A commercially available uric acid monitoring system that is chemically modified to reduce interference was evaluated via clinical evaluation for its performance and interference as compared to a centralized laboratory instrument.
Results: Precision was within ±3.1% for 3 levels of control solutions and whole blood samples. A range from 30 to 55% was acceptable for the measurement of hematocrit levels in whole blood samples. There was no interference for the potential substances at their high therapeutic levels. Hemolyzed samples of up to 75 g/l showed no interference with test results obtained by the BeneCheck system, while a −45.9% bias% was obtained during testing of the same samples by a spectrophotometer. Clinical evaluation showed that >95% of tests were within ±20% bias% compared to a centralized instrument in hospitals.
Conclusion: The uric acid monitoring system was suitable for use in monitoring or screening uric acid concentration for home users or professionals.

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1. Introduction

Uric acid is the end metabolism product of purine, purine being the nitrogen-containing component that occurs in nucleic acid. Uric acid is only slightly soluble in water and may precipitate out of solutions contributing to the formation of kidney stones. Uric acid measurement recently became important due to elevated levels which were observed in many patients with medical and health conditions [1–5] beyond gout [6].

In earlier days, uric acid was measured with the chemical reduction of photungstate complexes and involved a complicated process [7]. Uricase was used in specific catalysis of uric acid and enhanced the selectivity of uric acid determination [8]. Colorimetric procedures were the traditional technology for uric acid determination; either photungstate complexes or uricase catalysis to induce the chromophoric absorption change in the measurement process. Uricase methods with colorimetry or spectrophotometry are the most popular testing methods in use in clinical practice.

Electrochemistry technology was considered as a replacement for the spectrophotometer, based on the desire to reduce expensive equipment and to construct portable near patient devices [9,10].

Chemically modified screen printed electrode technology provided a new turning point for biochemical determination technology [11,12]. A non-enzymatic method, provided by chemically modified electrodes [13], was one of the most promising methods for uric acid determination, not only eliminating the problem of maintaining stability during enzyme preservation but also reducing the cost of supplying enzymes. Uric acid detection has become increasingly important for point of care and patients' self-monitoring. Currently, the majority of the portable uric acid monitoring devices on the market are mostly based on electrochemically modified technology.

According to the explanations of currently market available electrochemical uric acid monitoring systems, almost all are an application of the non-enzymatic method. Electrochemical uric acid testing methods are superior to the commercial enzymatic spectrophotometric method in several aspects: (1) a short detection time (normally <20 s for electrochemical method compared to about 10 min for spectrophotometric method); (2) no sample pretreatment step for electrochemical method;

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blood cells need to be removed for the spectrophotometric method due to interference caused by red blood cells; and (3) reagent (test strips) is stable for 18 months stored at room temperature for electrochemical method; but reagent for spectrophotometric method is only stable for 4 months and also requires refrigeration at temperatures of 2–8 °C after reconstitution. However, interference from many common medications and biological materials such as acetaminophen and ascorbic acid was the most common problem encountered when applying non-enzymatic method for uric acid measurement, due to the similarity of their chemical characteristics [10]. Although a list of materials that could potentially cause interference with test results is usually emphasized in the instruction manual of the uric acid monitoring system [14], this does not increase patient confidence during usage. Furthermore, there was not sufficient information studying the effects of interference for some devices [15].

2. Materials and methods

2.1. Materials

The BeneCheck PLUS multi-monitoring system for glucose, uric acid and total cholesterol (General Life Biotechnology) was used to evaluate the uric acid measurement function. The BeneCheck system contains test strips and a meter. The BeneCheck PLUS uric acid test strips were prepared by the General Life Biotechnology Co., Ltd using the chemically modified screen printed electrode technology to construct a two-electrode system with carbon paste as the working electrode and silver/silver chloride paste (Ecron) as the counter electrode. The working electrode surface was treated with 1.9 V for 15 s in a phosphate buffer (0.1 mol/l, pH 7.4). A passageway with a top cover from the tip of the strip to the electrodes was constructed for the strip to form a channel for capillary sample intake.

The uric acid measurement principle behind BeneCheck was based on amperometric electrochemistry. A whole blood sample is drawn by capillary action into the reaction zone of the strip. The uric acid in the whole blood is oxidized by the electrode, and a current proportional to the concentration of uric acid is detected by the meter when a fixed potential is applied across the electrodes. The current is then converted into a reading of uric acid concentration. The BeneCheck measuring range of uric acid is 30 mg/l to 200 mg/l, this range is wide enough to cover most patients. Sample volume required is 1 μl and measurement time is 15 s according to the instructions of the BeneCheck monitoring system.

BeneCheck PLUS meter used for uric acid determination is a palm size, battery-powered, light weight instrument designed for self-monitoring of capillary blood uric acid concentration.

Material used for the interference study included bilirubin, cholesterol, acetaminophen, creatinine, allopurinol, amiloride, atenolol, colchicine, diclofenac, gentisic acid, hypoxanthine, ibuprofen, metformin, tetracycline, tolazamide, tolbutamide and xanthine which were from Sigma. Glucose was from Baker. Ascorbic acid, hydrochloric acid and sodium hydroxide were from RDH while dopamine and methyl DOPA were from Aldrich. Glibenclamide, ketoprofen, L-tryptophan, sodium chloride, sodium L-lactate and sodium nitrite were from Sigma-Aldrich. Indomethacin and salicylate were from Fluka. Vacutainers with different anticoagulants including sodium heparin, sodium fluoride, sodium citrate and potassium EDTA were all from Becton Dickson.

2.2. Methods

2.2.1. Sample preparation

2.2.1.1. Uric acid stock solution preparation. Uric acid stock solution was prepared by adding uric acid powder (Sigma) into 0.08 mol/l of lithium carbonate solution (Sigma) to a concentration of 250 g/l.

2.2.1.2. Venous blood sample preparation. Venous blood samples were collected directly into vacutainer tubes containing heparin as an anticoagulant. Hematocrit of the blood sample was measured with Sysmex KX-21N automatic whole blood analyzer and the hematocrit of the sample was adjusted to 42.5 $\pm$ 0.5% by adding or removing plasma of the blood sample. The uric acid concentration of the venous blood sample was then adjusted by adding different volumes of the uric acid stock solution. The venous blood tubes were placed on a shaker for at least 30 min on gentle rotation.

2.3. Precision evaluation

Three levels of control solution with different uric acid concentrations provided by General Life Biotechnology were tested. Twenty-five replicates of each of the three level control solutions were measured by 1 meter. Three different concentrations of venous blood samples were prepared for precision evaluation. Five replicates of each concentration of samples were measured by 1 meter. Five meters were used for a total of 25 test results. The mean, standard deviation and the percentage of the coefficient of variation of the test results were calculated.

2.4. Hematocrit effect study

Venous blood samples with differing uric acid concentrations were prepared as previously described in the sample preparation method. According to the instructions for BeneCheck uric acid strips, acceptable hematocrit of blood samples ranges from 30% to 55% for uric acid measurement. The expected uric acid concentration for samples used in this hematocrit effect study was defined as 65 $\pm$ 10 mg/l, 100 $\pm$ 10 mg/l or 125 $\pm$ 10 mg/l, as measured by Cobas analyzer. For each uric acid concentration, venous blood was then aliquot to micro-centrifuge tubes and adjusted to different hematocrit concentrations ranging from 30% to 55% by adding plasma or removing plasma after centrifugation. The uric acid concentration in each tube was measured with a BeneCheck monitoring system. After measurement by the BeneCheck monitoring system, the hematocrit of the venous blood sample was measured with Sysmex KX-21N automatic whole blood analyzer. Samples were also centrifuged and the uric acid concentration of the plasma was measured with Cobas C111 chemistry analyzer.

2.5. Interference study

Studies were done to evaluate the interference caused by certain substances towards the BeneCheck Plus uric acid strip test results. Three categories of substances with the potential to cause interference: endogenous substances, exogenous substances, and preservatives, were involved in the study.

Concentrations of interference material in this study were prepared following NCCLS Document EP7-A2 guideline [16] or EP7-P [17] if the information was not in the EP7-A2 guideline. According to Appendix D of EP7-A2, the recommended test concentration (common pathological value) pH is 8.0, while the normal pH range of a blood sample is 6.8–7.8. Blood samples were adjusted to a pH of 6.8 with hydrochloric acid (0.6 mol/l) and a pH of 8.0 with sodium hydroxide solution (0.05 mol/l). The interference effect was evaluated for blood samples with a pH range of 6.8 to 8.0 by BeneCheck and Cobas.

Evaluation of anticoagulants was studied using 4 different commercial available vacutainers. Drawing venous blood into a 10 ml BD vacutainer with 158 USP U of sodium heparin to capacity resulted in a sample with a heparin concentration around 1580 USP U/dl, which was used as the standard reference for the uric acid sample. Venous blood from the same blood donor was injected into other BD vacutainers containing potassium EDTA (18.0 mg), sodium fluoride (17.5 mg) or sodium citrate (0.129 mol/l). Uric acid concentration in each tube was measured by BeneCheck and the bias% to the reference sample was calculated for each sample.

2.6. Effects of sample hemolysis

Venous blood samples were partially hemolyzed by extensive vortex or put in a refrigerator. The uric acid concentration of the original and partially hemolyzed blood samples were measured by BeneCheck. Then samples were centrifuged at 4000 rpm for 5 min, and then hemoglobin concentrations of the suspensions were measured with Sysmex KX-21N. The uric acid concentrations of suspensions were also measured by Cobas analyzer.

2.7. Ion strength study

Blood samples were aliquoted into 3 different micro-centrifuge tubes (1000 μl of venous blood in each tube) and centrifuged for 5 min. Different ion strength blood solutions were prepared by removing 200 μl of plasma supernatant from each tube and adding 200 μl of either 0, 154 or 200 mmol/l of sodium chloride aquatic solution. The blood sample in each tube was mixed gently then the uric acid concentration in each sample was measured using BeneCheck and Cobas analyzer.

2.8. Operation temperature study

BeneCheck meters and uric acid strips were incubated in a Low Temperature Incubator (Dengyng Instruments) for 30 min at the assigned operation temperature before the uric acid concentrations in the blood samples were measured.

2.9. Clinical validation with patient samples

This study was performed in Wan Fan Hospital, Taipei Medical University, Taipei, Taiwan. Out patients in the Wan Fan Hospital with adequate qualification were included in the study. Finger blood was tested for uric acid concentration using BeneCheck PLUS monitoring system and, within 5 min, the venous blood from the patient was drawn directly into 2 different vacutainer tubes. One tube contained heparin as an anticoagulant and the other vacutainer tube contained EDTA as an anticoagulant. Uric acid concentration of the venous blood within the heparinized tube was measured with the BeneCheck system, then the remaining sample within the tube was sent to the laboratory for the uric acid concentration to be measured using Beckman Coulter Analyzer (DxC 800). The venous blood sample contained within the tube with potassium EDTA was also sent to the laboratory and its hematocrit measured using Sysmex KX-21N. These studies were approved by the ethics committees of Taipei Medical University-Joint Institutional Review Board. All of the subjects signed an informed consent form before examination.

3. Results

3.1. Precision evaluation

Precision evaluation was studied with three levels of control solutions and three levels of venous whole blood samples. The average concentration was 50 mg/l for the first level of control solutions with a coefficient variation of 2.6%, calculated from 25 test results. The second level of control solutions had an average concentration of 75 mg/l which was obtained with a CV of 2.0%. The average concentration of the third level of control solutions was 124 mg/l with a CV of 2.5%. Venous blood samples were measured with 5 meters and a total of 25 test results were calculated for precision. The average concentration for the first level of venous whole blood samples was 45 mg/l with a CV of 2.9%. The second level of venous samples had an average concentration of 72 mg/l, calculated from the 25 test results with a CV of 3.1%. The average concentration of the third level of blood samples was 135 mg/l with a CV of 2.0%.

3.2. Hematocrit effect study

The different hematocrit samples were prepared from uric acid concentration adjusted venous whole blood. The uric acid concentration was measured by Cobas for confirmation that it was within the expected level, and hematocrit concentration of the prepared sample was also confirmed by Sysmex KX-21N prior to measurement with BeneCheck for the hematocrit effect study. From Table 1, the results showed that all bias% of uric acid measured by BeneCheck were less than ± 15% for samples with hematocrit concentration at 28.8% and 55.2% to the central of 42.4% of hematocrit reference, when uric acid concentration was 71 mg/l. However, when uric acid concentration was 89 or 120 mg/l, the bias% of uric acid concentration for samples with 28.8% of hematocrit was above 15%, compared to the reading of a sample with 42.4% hematocrit.

3.3. Interference study

The criteria for claiming no interference was defined as a bias% of less than ± 15% of uric acid concentration after the addition of an interference substance as compared to the original sample. Table 2 shows the summary of the interference study results. Several materials which therapeutic levels, reference levels or the suggested test concentrations were not listed in the EP7-A or EP7-P were tested at a concentration that was above the high range of clinically recommended dosing.

Acetaminophen showed a high interference at the suggested test concentration (200 mg/l), but with a bias% of only 13.7% at the high concentration of therapeutic range (30 mg/l). Total cholesterol suggested that test concentration was 5030 mg/l according to EP7-A, however, the concentration of cholesterol that was added to the samples for the evaluation was 3220 mg/l, due to the fact that the total cholesterol concentration was 1850 mg/l in the original venous blood sample preparation. Sugars, not only glucose but also others such as maltose, sucrose, and xylose, were all tested at a level of 10 g/l, following the suggestion in EP7-A for glucose inference studies. No interference was noted when blood samples of different pH values in the range of pH 6.8 to 8.0 were tested by BeneCheck.

Table 3 shows the interference study using BD vacutainers containing different anticoagulants. Samples containing uric acid at a concentration of 57 mg/l in a heparinized tube, measured with BeneCheck, were used as the standard reference to calculate the bias% of other anticoagulants. A bias of 16.1% from samples contained in sodium fluoride tubes indicated that sodium fluoride anticoagulant would give a higher uric acid concentration if measured by BeneCheck. EDTA presented a bias of − 3.4% of uric acid concentration while sodium citrate presented a bias of − 10.4% of uric acid concentration to the standard reference heparin sample.

Hemolyzed blood samples with 0, 9 and 75 g/l hemoglobin in the suspension were obtained by Sysmex measurement for hemoglobin

Table 1
Hematocrit effect of uric acid measurement with BeneCheck.

UA, mg/l at Hct 42.4%	Hct%		
	28.8	34.5	55.2
71	79	76	63
CV%	3.1	1.9	2.9
Bias% to Hct 42.4%	11.4	6.3	− 12
89	103	96	79
CV%	1.5	1.9	3.0
Bias% to Hct 42.4%	16.1	7.4	− 11
120	139	125	106
CV%	1.8	2.6	2.2
Bias% to Hct 42.4%	15.6	3.9	− 11.6

UA: uric acid; Hct: hematocrit; Bias% to Hct 42.4%: uric acid reading at different Hct% bias% to the uric acid reading at 42.4% of Hct.

Table 2
Summary of interference study results.

Interference material	Additive concentration, mg/l	Original uric acid concentration, mg/l	Interference, bias%	Therapeutic/reference concentration, mg/l	Suggested test concentration, mg/l
Acetaminophen	30	73	13.7	10–30	200
Allopurinol	100	62	−2.6	5–20	40
Amiloride	10	62	−12.9	No data	
Ascorbic acid	60	74	9.8	4–20	60
Atenolol	100	67	4.8	0.2–2	10
Bilirubin	200	75	2	2	200
Cholesterol	3220	57	0	1140–2010	5030
Colchicine	100	67	7.4	No data	
Creatinine	100	67	9.8	6–13	50
Diclofenac	50	67	−7.1	No data	
Dopamine	1.1	73	−2.5	0.3	0.9
Ephedrine	100	70	4.3	No data	
Galactose	160	72	−2.5	<0.5	1.5
Gentisic acid	18	73	6.5	2–6	18
Glibenclamide	800	62	−3.9	No data	
Glucose	10,000	67	−5.7	740–1060	9900
Hypoxanthine	10	47	2.1	No data	
Ibuprofen	500	67	−1.5	10–70	500
Indomethacin	200	62	1	5–18	36
Ketoprofen	200	62	1.3	No data	
Lactate	603	60	−2.2	45–198	594
D-Maltose	10,000	69	−2.5	No data	
Mannitol	10,000	68	−4.7	No data	
Metformin	400	67	1.2	4	40
Methyl DOPA	25	75	6.7	1–5	25
Nitrite	30	58	0.6	No data	
Salicylate	500	62	3.2	0.1–0.3	0.6
Sucrose	10,000	70	−4.6	No data	
Tetracycline	15	71	−1.1	2–5	15
Tolazamide	250	62	8.7	No data	
Tolbutamide	400	62	4.2	0.05–0.1	0.6
Tryptophan	150	54	1.2	No data	
Xanthine	10	51	2.0	No data	
Xylitol	10,000	69	−2.3	No data	
Xylose	10,000	69	−1	No data	
pH	6.8	55	3.6	7.11–7.45	Cobas value used as the reference
	7.6	75	−6.7		
	8.0	69	1.4		

concentration after centrifugation. Uric acid concentrations were measured by BeneCheck, which revealed that the uric acid concentration bias% was within −3.1% for all hemolyzed samples. However, the uric acid concentration bias% was −45.9% for samples with 75 g/l lysed hemoglobin when the suspensions were measured by Cobas.

3.4. Ion strength study

Based on the assumption that the ion strength of the original blood sample should be near 150 mmol/l, the ion strength of the sample added water would be near 97.4 mmol/l, while the sample with the addition of 200 mmol/l of sodium chloride solution would be near 167.5 mmol/l. The sample with 150 mmol/l of sodium chloride solution added was used as control. The concentration of uric acid of the sample with 97.4 mmol/l (82 mg/l) ion strength, when measured by BeneCheck, was decreased by 3.75% compared to the control sample (85 mg/l). The measured uric acid concentration of the sample with ion strength of 167.5 mmol/l (84 mg/l) was slightly lower than the control sample.

Table 3
Interference study using BD vacutainers with different anticoagulants.

Anticoagulant	Heparin	NaF	EDTA	Citrate
Mean (UA), mg/l	57	66	55	51
CV%	3.40%	2.90%	4.00%	3.70%
Bias% to reference	Reference	16.1	−3.4	−10.4

3.5. Operation temperature study

According to the user manual of the BeneCheck uric acid monitoring system, the operation temperature range is from 10 °C to 40 °C. The meter will not be activated when a strip is inserted if the environmental temperature is lower than 10 °C or higher than 40 °C. The assigned test temperatures were 5, 10, 24.5, 40 and 42.5 °C. The meter did not respond when a strip was inserted into the strip holder of the meter at temperatures of 4.7 and 42.5 °C. Table 4 shows the effects of operation temperatures. There was no significant effect on test results between test temperatures of 24.5 and 39.5 °C, but a −16.9% bias% for uric acid concentration of 39 mg/l and a −11.0% bias% for uric acid concentration of 182 mg/l were noted at test temperatures of 10.8 °C when compared to temperatures of 24.5 °C.

3.6. Clinical evaluation

Hematocrit concentrations ranging between 30% and 55% was a criteria for sample acceptance, based on the BeneCheck uric acid

Table 4
Effects of operation temperature.

Operation temperature	10.8 °C		24.5 °C		39.5 °C	
UA mg/l Cobas	39	182	39	178	39	174
UA mg/l BeneCheck	32.4	162	38.4	175.4	39.6	168.8
Bias% to Cobas	−16.9	−11.0	−1.5	−1.5	1.5	−3.0

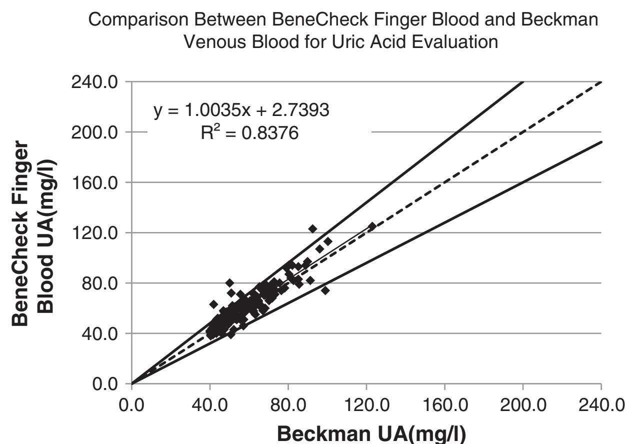

Fig. 1. Comparison between finger blood with BeneCheck and venous blood with Beckman Coulter.

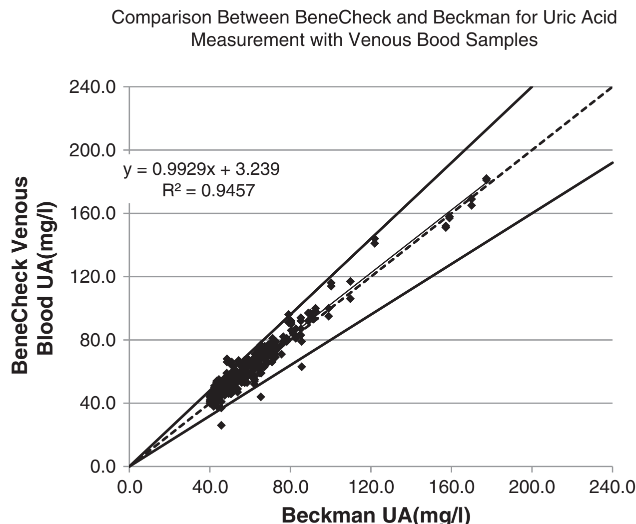

Fig. 2. Comparison between BeneCheck and Beckman for uric acid measurement with venous blood samples.

monitoring system's limitations in uric acid measurement. Samples with a uric acid concentration lower than 40 mg/l were also removed from comparison as the bias% may have easily become large. Uric acid concentration in finger blood was measured with the BeneCheck system, and the venous blood from the same patient was measured with the Beckman analyzer. A total of 187 samples were collected. The uric acid concentration range in the finger blood study was from 40 mg/l to 123 mg/l, based on the results from venous blood samples collected from the same subject measured with Beckman. Results of the regression line equation for a total of 187 samples showed a slope of 1.0035 with a positive intercept of 2.739 mg/l and the coefficient of determination (R^2) was 0.8376. Fig. 1 shows the testing comparison of finger blood samples measured by BeneCheck and venous samples measured by Beckman. The number of tested results that remained within a ±5% bias between BeneCheck and Beckman was 70 tests out of a total of 187 tests (37.4%), 131 tests out of 187 tests (70.1%) were within a ±10% of bias and 161 tests (86.1%) were within a ±15% bias. There were 178 tests (95.2%) within ±20%. The above data is shown in Table 5.

Venous blood samples with high uric acid concentrations were prepared in order to compare the higher ranges of measurement testing results by BeneCheck and Beckman. The range of uric acid values, according to test results by Beckman, was 40 to 177 mg/l. Results of the regression line equation for a total of 380 samples showed a slope of 0.9929 with a positive intercept of 3.239 mg/l and a coefficient of determination (R^2) of 0.9457. Fig. 2 shows the correlation of uric acid concentration in venous blood measured by BeneCheck and Beckman.

The number of tested results that remained within a ±5% bias between BeneCheck and Beckman was 157 tests out of a total of 380 tests (41.3%), 275 tests out of 380 tests (72.4%) were within a ±10% of bias and 336 tests (88.4%) were within a ±15% bias. 364 tests (95.8%) had a bias% within ±20%. The above data is shown in Table 6.

Finger blood and venous blood from the same subject were both measured by BeneCheck. The uric acid concentration range was 40 mg/l to 123 mg/l. A correlation comparison was plotted in Fig. 3. A linear regression of the uric acid concentration in finger blood to the concentration in venous blood, $Y = 0.9611\ X + 2.8095$ (R^2 was 0.8865) was obtained.

Table 5
Percentage of test number by BeneCheck within different bias% ranges to Beckman Coulter. Finger blood samples measured with BeneCheck and ` by Beckman.

Bias% to Beckman	≦±5%	≦±10%	≦±15%	≦±20%
Test number/total number	70/187	131/187	161/187	178/187
Percentage%	37.4%	70.1%	86.1%	95.2%

4. Discussion

Precision study showed three levels of control solutions and 3 levels of venous whole blood samples, each with 25 tests performed by 5 different meters. All coefficient variations were within the range of 2.0% to 3.1% for all levels of samples and concluded that there was no difference in meter variability. Samples with higher uric acid concentrations showed a tendency of higher bias% at the lower hematocrit range but less bias% at the higher hematocrit range compared to the central hematocrit level of 42.5%.

Acetaminophen showed a high level of interference (66.8%) at the suggested test concentration of 200 mg/l for a sample with uric acid concentrations of 73 mg/l, however, minimal interference (13.7%) was noted at a high therapeutic concentration (30 mg/l), according to the definition of less than ±15% of bias% to the original uric acid concentration. It is suggested that the uric acid measurement in patients taking acetaminophen following a strict dosage request would not be affected using BeneCheck. Methyl DOPA caused a 6.7% increase of uric acid concentration at a concentration level of 25 mg/l, however, a −22.7% interference was found if measured by Cobas. We assume that chromogenic reagents interfere severely with the detection method used by a spectrophotometer. A similar explanation was concluded and confirmed for hemolyzed samples causing higher interference if measured by method of a spectrophotometer [18].

Anticoagulant study results have suggested that vacutainers containing heparin or EDTA as the anticoagulant can be used for uric acid measurement by BeneCheck. Sodium fluoride or citrate should be avoided as NaF might produce a higher uric acid result, while a lower uric acid result may be obtained if citrate is used as an anticoagulant.

Measurement of samples with a uric acid concentration of 39 mg/l at operation temperatures of 10.8 °C showed a −16.9% bias compared to an operation temperature of 24.5 °C. It suggested that negative interference would occur if BeneCheck is used to test samples containing low uric acid concentrations at temperatures near 10 °C.

Table 6
Percentage of test number by BeneCheck within different bias% ranges to Beckman Coulter. Venous whole blood samples measured with BeneCheck and plasma from venous blood samples measured by Beckman.

Bias% to Beckman	≦±5%	≦±10%	≦±15%	≦±20%
Test number/total number	157/380	275/380	336/380	364/380
Percentage%	41.3%	72.4%	88.4%	95.8%

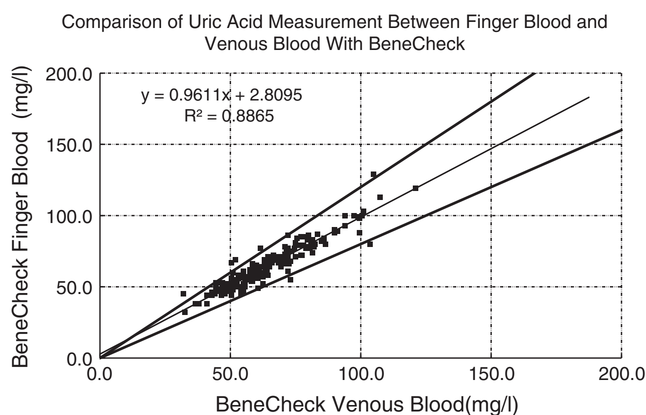

Fig. 3. Comparison of uric acid measurement between finger blood and venous blood with BeneCheck.

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