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Research Article

Evaluation of analytical performance of two iPTH immunoassay methods in hemodialysis patients

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Abstract

Objectives: Renal excretion of parathormone (PTH) C-terminal fragments can cause an accumulation of the C-terminal form in the blood in chronic kidney disease patients. Thus, the measurement of the active form of PTH has become important. This study was designed to compare the Architect iPTH test measured using the Architect i2000SR System (Abbott Laboratories, Lake Bluff, IL, USA) and the Beckman iPTH test measured using the Beckman Coulter Dxi 800 (Beckman Coulter, Brea, CA, USA), which are 2 immunoassay systems commonly used in routine laboratory analyses, and to evaluate the analytical performance in hemodialysis patients.

Methods: The immunoassays were assessed for accuracy, precision, limit of blank (LoB), limit of detection (LoD), and limit of quantification (LoQ).

Results: A total of 86 samples were run on both systems and the correlation between the methods was evaluated. The i2000SR and Dxi 800 assays demonstrated good performance in terms of precision, accuracy, LoB, LoD, and LoQ. Intra-class correlation coefficient analysis revealed a difference of 0.912 (0.489-0.968) with a y=2.58+1.53x equation.

Conclusion: It was confirmed that these analyzers widely used for iPTH measurement operate at an acceptable level of analytical performance. It was observed that the measurements obtained from both analyzers were consistent, but the Abbott Architect i2000SR provided higher results than the Beckman Coulter Dxi800. For consistency, is suggested that patient follow-up should be performed using the same kits, the same analysis system, and in the same laboratory.

Keywords: Clinical laboratory techniques, evaluation studies, immunoassay, method comparison parathyroid hormone

Parathormone (PTH) is a peptide synthesized as an 115-amino acid preprohormone in the parathyroid gland in response to a decreased serum calcium level and is used as a marker for chronic kidney disease mineral and bone disorder (CKD-MBD) [1]. PTH is synthesized as a pre-prohormone as a linear protein of 84 amino acids and the remainder is known as intact PTH (iPTH). iPTH rapidly breaks down in the blood to yield N-terminal and C-terminal fragments of 34-amino acid. PTH can be present in the blood in 3 forms: iPTH, N-terminal, and C-terminal. The iPTH and N-terminal forms are biologically active, but have a short half-life. C-terminal fragments, however, are an inactive form and have a longer half-life than iPTH. PTH is metabolized mainly in the kidneys and the liver. The kidneys play an important role in the excretion of inactive fragments [2]. Eighty percent of blood PTH in normal patients and approximately 95% of blood PTH in chronic kidney disease (CKD) patients is in the C-terminal form. Renal excretion of C-terminal fragments causes an accumulation of the C-terminal form in the blood in CKD patients [3]. The measurement of the accumulated

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C-terminal form of PTH can overestimate the degree of secondary hyperparathyroidism in CKD patients. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend maintaining an iPTH level 2-9 times the URL for patients with CKD [4]. Thus, the measurement of the active form of PTH has become an important concern [5].

As a result of years of studies, several kits have been developed to measure the active form of PTH. Since the first-generation kits developed used antibodies against the C-terminal of PTH; they measured not only active iPTH, but also inactive forms. They were then replaced with two-zone immunoassay kits, called the second-generation, or iPTH kits, which use antibodies bound to both the N-terminal and the C-terminal. Subsequently, however, it was shown that these kits measured inactive N-terminal fragments and missed the first 4-7 amino acid N-terminal fragments [6]. Therefore, new kits, called biointact PTH kits or third-generation kits, were developed using a signaling antibody directed against the 1-4 amino acid positions of the N-terminal [7]. In our country, second-generation kits are commonly used for iPTH measurement.

The use of different antibodies in immunoassay methods and the lack of a reference method for measurement has reduced comparability between methods [8]. It has also been demonstrated that there are many pre-analytical factors affecting iPTH measurement [9, 10]. These factors make it difficult to standardize iPTH measurement and to use it in treatment follow-up.

The present study was carried out to compare the results of the Architect iPTH test (AiPTH) measured using the Architect i2000SR system (Abbott Laboratories, Lake Bluff, IL, USA) and the Beckman iPTH test (BiPTH) measured using the Beckman Coulter Dxi 800 analyzer (Beckman Coulter, Brea, CA, USA), which are 2 immunoassay systems commonly used in routine laboratories, and to evaluate their analytical performance in hemodialysis patients.

Materials and Methods

Samples

This analytic performance evaluation used blood samples from 45 dialysis patients who were treated and followed up regularly in the hemodialysis unit of a single hospital and had a request for an iPTH test. A control group (Group 1) was formed of patients with low, normal, and high iPTH levels among samples from patients without CKD. A total of 41 serum samples were selected from those taken from non-hospitalized adult patients (aged >18 years) with normal liver and kidney function test results and no leukocytosis. The dialysis patient sample was identified as Group 2. All of the blood samples were drawn from the antecubital vein between 8:00-10:00 am after a night of fasting using 5-mL BD Vacutainer SST II Advance Plus Blood Collection Tubes (lot 7327531; Becton, Dickinson and Company, Franklin Lakes, NJ, USA), serum-separating tubes with yellow caps. The serum samples used for iPTH analysis were all drawn according to standard pre-analytical protocols. In Group 1, 15 samples had an iPTH value of 1-15 pg/mL; 15 samples were selected with a measurement 15-68.3 pg/mL, and in 11 samples it was >69 pg/mL. Ethics approval for this study was obtained from the Clinical Research Ethics Committee of Bolu Abant Izzet Baysal University on 05.07.2018 (no: 2018/113).

Laboratory measurements

The iPTH measurements were made on the same day using the Architect i2000SR System analyzer (AiPTH) and the Beckman Coulter Dxi 800 analyzer (BiPTH). Second-generation iPTH kits were used in both systems. The upper range limit (URL) of AiPTH and BiPTH was 68.3 pg/mL and 88.0 pg/mL, respectively, and the reportable range for AiPTH and BiPTH was 3.0-3000.0 pg/mL and 1.0-3500 pg/mL, respectively. All of the research was performed according to the evaluation protocols of the Clinical Laboratory Standards Institute (CLSI) that are specific to each parameter [11–13].

Analytical performance studies

Accuracy

Three references from the 13th immunoassay report period of the Association of Clinical Biochemistry Specialists External Quality Control Program (KBUDEK) 2018 were used for the accuracy evaluation. The target mean values for the external quality control materials of this period were 4.925 pg/mL-1420.9579 pg/mL, which were within the reportable measuring ranges declared by the manufacturers. The average bias of the data obtained using the AiPTH and BiPTH was calculated based on the percentage bias taken from the KBUDEK program [13, 14]. The percent bias from the published target means was calculated using the formula of 100 x (measured result-mean)/mean. The acceptable accuracy value used was <8.8%, the specification for inaccuracy [15].

Precision

The data calculated in this study were used instead of the precision data in the Abbott and Beckman Coulter instructions. The precision, within-run, between-run, and between-day variation was calculated using the mean and SD values obtained by consecutive and intermittent measurements repeated every day over 20 days. All of the analyses were carried out in accordance with the manufacturers' instructions.

Architect iPTH internal quality control samples (Multichem IA Plus Ref. 05P76-10, Lot no. 37104170; Technopath Clinical Diagnostics, Ballina, Co. Tipperary, Ireland) were used in precision runs. The within-run precision was determined at concentrations of 10.0±2 pg/mL, 65.05±11.37 pg/mL, and 250.0±43.75 pg/mL after 20 consecutive runs with this tri-level internal quality control material, and the between-run precision was determined after 20 intermittent runs using

these quality control samples within 1 day. The between-day precision was determined using the tri-level quality control samples and the reactive from the same lot in the same analyzer over 20 days [12, 14].

For BiPTH, the Dxi 800 iPTH internal quality control samples (Autonorm Lyo L-1, Ref. 212405, Lot.1608805 and Autonorm Lyo L-2, Ref. 212505, Lot.1609806; SERO AS, Stasjonsveien 44 NO-1396 Billingstad, Norway) were used in the precision runs. The within-run precision was determined at concentrations of 17±2.2 pg/mL and 91.5±11.05 pg/mL after 20 consecutive runs with these 2 internal quality control samples. The between-run precision was determined after 20 intermittent runs with these internal quality control samples within 1 day. The between-day precision was determined using the two-level system of internal quality control and the reactive from the same lot in the same analyzer over 20 days [12, 14]. Total precision was compared with the manufacturer's claims. For AiPTH, the manufacturer stated that they had developed the product to be ≤9% for low control and ≤7% for medium and high control total coefficient of variation (CV). For BiPTH, the manufacturer stated that they developed the product to display ≤8% total CV.

Limit of blank, limit of detection, and limit of quantification

The study was carried out according to the recommendations of the CLSI EP17-A2 document [11]. The limit of blank (LoB) was determined by running the zero calibrator of the manufacturer 20 times using the LoB=Mean (Blank)+1.645*SD(Blank) formula. The limit of detection (LoD) was determined by running a sample with the lowest concentration 20 times, which were prepared with 0.5 dilution, using the smallest non-zero calibrator and LoD=LoB+1.645*SD (control with low concentration). The samples were prepared at concentrations close to the limits specified by the analyte manufacturers. The limit of quantification (LoQ) was determined by taking the smallest values within a CV ≤20% [11, 14].

Method comparison

The method comparison runs were carried out according to the guidance in the CLSI EP9-A3 document. AiPTH and BiPTH were used in the Group 1 and Group 2 serum samples [13, 14]. A Bland-Altman plot was drawn and Passing-Bablok regression analysis was performed.

Statistical analysis

Mean and SD for numerical variables and number and percentage values of categorical variables were given as descriptive statistics. The correlation between the 2 immunoassay measurement methods was interpreted using the intraclass correlation coefficient (ICC). ICC values of <0.50 were considered poor, 0.50-0.75 intermediate, 0.76-0.90 moderate, and >0.90 excellent reliability ratings [16]. Since no information on whether there is a systematic and/or proportional error between ICC value and methods was provided, Passing and Bablok regression analysis and a Bland-Altman graph were used to evaluate the measurement errors between the methods. The measurement errors were evaluated according to 95% confidence interval results of the regression model coefficients. Among the model coefficients, the constant that does not include the zero value of the confidence interval indicates the presence of a proportional error, and the slope that does not include any value of the confidence interval indicates the presence of a systematic error. The analyses were carried out using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) and MedCalc Statistical Software version 11.3.0 (MedCalc Software bv, Ostend, Belgium). The significance level was accepted as $p<0.05$. The CV% value was calculated using the manufacturers' internal quality control materials. The percent bias value was calculated as a systematic difference between the mean of the results obtained using the reference method and the mean of the test results of this study [17, 18].

Results

The median (min-max) AiPTH values obtained for Group 1 were 59 pg/mL (3-227 pg/mL) and 456.5 pg/mL (15.2-1160.5 pg/mL) for Group 2, while the BiPTH values for Group 1 were 33.3 pg/mL (1-130.4 pg/mL) and 284 pg/mL (7.9-801.5 pg/mL) for Group 2. The performance characteristics for the AiPTH and BiPTH measurements are given in Table 1. Good accuracy studies use inaccuracy <8.8% as a comparison with a desirable specification. In our study, the between-day CV% values were 4.37-7.68%, the within-run CV% values were 3.60-4.33%, and the between-run CV% values were 7.09-7.60% for the tri-level AiPTH control. Overall, the CVs were compatible with the manufacturers' claims.

The correlation between the 2 methods was evaluated using the ICC, and the ICC values for Group 1, Group 2, and the total were 0.809 (0.648-0.893), 0.818 (0.661-0.903), and 0.912 (0.489-0.968), respectively. In order to examine the measurement errors between methods, Passing and Bablok regression analysis and a Bland-Altman plot were used, as seen in Figure 1 and Figure 2. According to the results, no deviation from linearity existed between the methods (CUSUM test p=0.18) and a y=2.58+1.53x equation was obtained as a result of the Passing and Bablok regression analysis.

To evaluate the clinical effect of the 2 assays, the results obtained from the instruments were categorized. The Group 1 results from both assays were divided into 2 groups: normal and elevated PTH levels, according to the recommended the URL for PTH of the manufacturer. Twelve of 41 (29.3%) of results were high in the AiPTH assay and normal in the BiPTH assay. Twenty-six of 41 results were normal in both assays, and 3 of 41 results were measured as high on both assays. The Group 2 results from both assays were divided into 2 groups: higher or lower than 9 times the URL of the iPTH pg/mL levels.

Table 1. Performance characteristics of intact parathyroid hormone testing

Performance criteria			AiPTH	BiPTH
Accuracy (% bias)			4.23	4.67
LoB (pg/mL)			0.31	0.42
LoD (pg/mL)			0.85	1.04
LoQ (pg/mL)			2.4	5.0
Precision				
Within-run				
SD	(0.403-2.22-9.78)†	(4.44-4.30)*		
Mean	(9.84-61.58-225.67)†	(18.02-93.91)*		
CV%	(4.09-3.60-4.33)†	(4.44-4.30)*		
Between-run				
SD	(0.70-4.83-16.48)†	(0.69-3.22)*		
Mean	(10-63.54-229.71)†	(17.97-92.15)*		
CV%	(7.09-7.60-7.17)†	(3.85-3.50)*		
Between-day				
SD	(0.76-5.31-11.5)†	(1.08-6.68) *		
Mean	(10.18-69.21-263.28)†	(17.67-94.47)*		
CV%	(7.49-7.68-4.37)†	(6.12-7.07)*		

†Architect iPTH internal quality control: Multichem IA Plus (Ref. 05P76-10, Lot no. 37104170; Technopath Clinical Diagnostics, Ballina, Co. Tipperary, Ireland). Levels: 10±2-65.05±11.37-250±43.75. *Dxi 800 iPTH internal quality control: Autonorm Lyo L-1, Ref. 212405, Lot.1608805 and Autonorm Lyo L-2, Ref. 212505, Lot.1609806; (SERO AS, Billingstad, Norway). AB Scientific, London, England). Levels: 17±2.2-91.5±11.05. AiPTH: Architect iPTH test measured using Architect i2000SR System (Abbott Laboratories, Lake Bluff, IL, USA); BiPTH: Beckman iPTH test measured using the Beckman Coulter Dxi 800 analyzer (Beckman Coulter, Brea, CA, USA); LoB: Limit of blank; LoD: Limit of detection; LoQ: Limit of quantification.

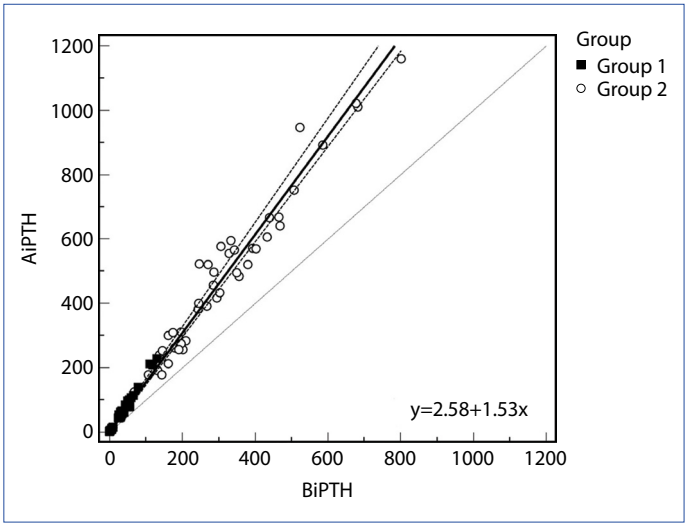

Figure 1. Passing-Bablok regression analysis of 2 intact parathyroid hormone (iPTH) immunoassays. Group 1 is the control group, Group 2 is the dialysis patient sample group. The regression equation is presented as y=a+bx (a is the regression line's intercept and b is the regression line's slope).

AiPTH: Architect iPTH test measured using Architect i2000SR System (Abbott Laboratories, Lake Bluff, IL, USA); BiPTH: Beckman iPTH test measured using the Beckman Coulter Dxi 800 analyzer (Beckman Coulter, Brea, CA, USA).

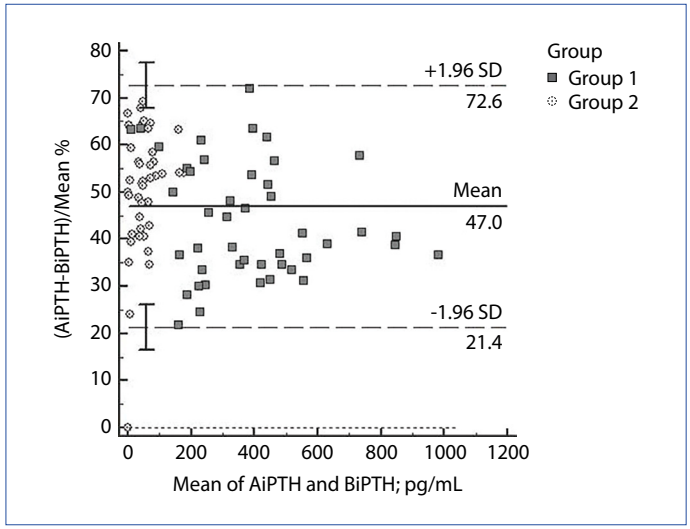

Figure 2. Bland-Altman plot of method comparison of 2 intact parathyroid hormone (iPTH) immunoassays. Group 1 is the control group, Group 2 is the dialysis patient sample group.

AiPTH: Architect iPTH test measured using Architect i2000SR System (Abbott Laboratories, Lake Bluff, IL, USA); BiPTH: Beckman iPTH test measured using the Beckman Coulter Dxi 800 analyzer (Beckman Coulter, Brea, CA, USA).

In Group 2, while 1/45 (2.2%) BiPTH results was higher than 9 times the URL of iPTH pg/mL, 9/45 (20%) AiPTH results were higher than the URL.

Discussion

Good performance was obtained in our iPTH test accuracy studies with measurements made with the Architect i2000SR system and the Dxi 800 system, which are widely used im-

munoassay systems in routine laboratories. In order to investigate the coefficient of correlation between the methods, the ICC was examined and there was a similar and good level of agreement in both groups; however, a perfect agreement was obtained when both groups were evaluated together. According to our results, there was no deviation from linearity between the methods. Therefore, Passing and Bablok regression analysis and a Bland-Altman graph were used to examine the measurement errors between the methods. The results of the regression analysis revealed both a proportional and systematic error/difference between the AiPTH and BiPTH methods. It was determined that the AiPTH method yielded a proportionally higher measurement value compared with the BiPTH method. The repeatability values and accuracy were acceptable for both methods. The LoB, LoD, and LoQ results in our study were consistent with the manufacturers' data.

In a 2017 study conducted by Esther et al. [19], 2 iPTH kits were compared using the Siemens ADVIA Centaur XP instrument (Siemens Healthineers GmbH, Erlangen, Germany) and the CV% was found to be 2.31-6.23%. We also obtained a CV% of 3-7%. The results were consistent with the current study in terms of precision.

In a study performed by Eddington et al. [5] in 2014, they used 17 different laboratories, 8 different methods, and 7 instruments for 37 patients with CKD, and they found that there were significant differences between the instruments, with the Abbott Architect instrument yielding the highest PTH values. In 2013, Tan et al. [7] compared a COBAS Elecsys instrument (Roche Diagnostics, Basel, Switzerland) with 4 instruments, including the Abbott i4000SR and the Beckman Coulter Access2 for 83 patients with CKD and observed that there were significant differences between the kits, with higher results from the Abbott instrument. In our study, it was also found that the AiPTH results were higher than those obtained using BiPTH. The higher AiPTH results in Group 2 were notable.

In CKD, decreased renal excretion of C-terminal PTH fragments causes accumulation of these fragments in the circulation [3]. Variation in the antibody used by assays, which recognize different fragments, results in differences in PTH measurements. This makes it difficult to maintain appropriate follow-up of a patient and comparability of results from different hospitals. KDIGO recommends that a patient requiring dialysis maintain a PTH level in the range of 2-9 times the URL. Although this a wide range, a study conducted with 149 patients with CKD found that 26.8% of the PTH levels were more than 9 times the URL when measured with the Abbott Architect while it was 8.1% for the Beckman Access system (Beckman Coulter, Inc., Brea, CA, USA) [20]. Similarly, in the present study, 29.3% of results were higher than 9 times the URL with AiPTH, while it was 2.2% with BiPTH. Thus, KDIGO recommends using the trend of PTH to guide treatment [4].

In a study performed by Einbinder et al. [21] in 2017, iPTH and biointact PTH kits were compared in patients with non-dialysis CKD and as expected, the biointact PTH results were lower. Although PTH measurement with biointact PTH is effective, since it targets the first few amino acids at the N-terminal end, it is not yet widely used, either in our country or globally. Almond et al. [22] highlighted that bias differences between methods are caused by the use of antibodies with different sensitivities in commercial kits. The higher AiPTH results in our study may have been caused by the use of different antibodies, which might be eliminated with widespread use of third-generation kits.

In a systematic review performed by Hanon et al. [9] in 2013, it was stated that iPTH measurement is more stable in a tube containing ethylenediaminetetraacetic acid. A limitation to our study was the use serum separator tubes with a yellow top, which are already used in iPTH measurement in our laboratories. A limited patient count is another constraint.

Conclusion

It was confirmed that the Abbott Architect i2000SR and the Beckman Coulter Dxi 800 analyzers widely used for iPTH measurement operate with acceptable analytical performance. It was observed that the measurement results obtained from these 2 analyzers were consistent, but the Abbott Architect i2000SR had higher results than the Beckman Coulter Dxi 800. In conclusion, it is suggested that the growing use of iPTH testing requires support in order to obtain consistent results from different laboratories and provide harmonization. Until then, follow-up of CKD patients should be performed using the same kits, the same analysis system, and in the same laboratory.

Conflict of interest: There is no conflict of interest between the authors.

Ethics Committee Approval: This study was approved by Bolu Abant Izzet Baysal University Clinical Researches Ethics Committee (Date:05.07.2018 and No: 2018/113).

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