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Gabriella Bekő, Henriett Butz, Klára Berta, András Tislér, Ferenc Olajos, Barna Vásárhelyi and Attila Patócs*

Switching between parathormone (PTH) assays: the impact on the diagnosis of renal osteodystrophy

Abstract

Background: Clinical guidelines for decision-making in chronic kidney disease (CKD) consider parathormone (PTH) levels. The measured PTH values differ if novel full length PTH(1-84) assays are used instead of earlier intact iPTH assays. In this study we analyzed how the classification of CKD patients alters when iPTH assays are switched to PTH(1-84) assays.

Methods: Plasma samples were collected prior to dialysis sessions from 110 consecutive CKD patients on maintenance hemodialysis. PTH levels were determined with iPTH assays (Elecsys, Architect and DiaSorin Liaison N-tact) and PTH(1-84) assays (Elecsys and Liaison). Using KDIGO guidelines patients were classified as being below, above and in the recommended target range (RTR) of PTH. The results of classification with different assays were evaluated and, a novel calculation method of RTR was implemented.

Results: The prevalence of patients with PTH in RTR is comparable with each assay, but the individual patients differed. PTH(1-84) Elecsys and Liaison assays classified more patients as being below RTR than iPTH Elecsys and Architect but not Liaison N-tact assay (27.3%, 22.7% vs. 41%, 31.8%, and 36.4%, respectively). In turn, PTH(1-84) Elecsys and Liaison assays identified less CKD patients with PTH above the RTR than iPTH except N-tact assays (6.4%, 10% vs. 16.3%, 19%, and 6.3%, respectively). Using our calculation method, our discrimination values for PTH(1-84) assays to achieve classification identical to that with iPTH Elecsys were lower than those recommended by the manufacturer.

Conclusions: Current guidelines for the treatment of secondary hyperparathyroidism in CKD should consider the type of assays used for PTH measurement. Each laboratory should assess its own RTR for PTH tests to achieve comparable classification. The presented calculation is simple, it mimics an everyday situation, switching from one assay to another one, and provides useful RTR values for PTH tests.

Keywords: chronic kidney disease; dialysis; intact PTH; parathormone (PTH) measurement; PTH(1-84); secondary hyperparathyroidism.

***Corresponding author: Dr. Attila Patócs,** MD, MSc, PhD, Department of Laboratory Medicine Institute, Central Isotope Laboratory, Semmelweis University 1088 Budapest, Szentkirályi u. 46, Hungary, Phone: +36 1 2660926 ext 55577, Fax: +36 1 2664616, E-mail: patatt@bel2.sote.hu
Gabriella Bekő and Ferenc Olajos: Department of Laboratory Medicine Institute, Semmelweis University, Budapest, Hungary
Henriett Butz: Department of Laboratory Medicine Institute, Semmelweis University, Budapest, Hungary; and Molecular Medicine Research Group, Hungarian Academy of Sciences and Semmelweis University, Budapest, Hungary
Klára Berta: Fresenius Medical Care, Budapest, Hungary
András Tislér: 1st Department of Medicine, Semmelweis University, Budapest, Hungary
Barna Vásárhelyi: Department of Laboratory Medicine Institute, Semmelweis University, Budapest, Hungary; and Research Group of Pediatrics and Nephrology, Hungarian Academy of Sciences and Semmelweis University, Budapest, Hungary
Attila Patócs: Molecular Medicine Research Group, Hungarian Academy of Sciences and Semmelweis University, Budapest, Hungary

Introduction

Parathyroid hormone or parathormone (PTH) is an 84 amino acid-long polypeptide hormone produced in parathyroid glands. Its blood level is regulated mainly by blood ionized calcium concentration with low extracellular calcium levels promoting (1-84)PTH secretion. An important point of regulation is the enhanced proteolysis of (1-84)PTH. Although N-terminal PTH fragments are traditionally considered to be inactive, the C terminal fragmented (7–84)PTH molecules may inhibit PTH action [1].

PTH levels are routinely measured to monitor the progression of secondary hyperparathyroidism (sHPT) in patients with chronic kidney disease (CKD). Several

preanalytical and analytical factors affect the results of PTH analysis [2–4]. The method used for PTH detection also affects PTH results. Up to a 2.7- to 4-fold difference in PTH values were reported with different assays when samples of CKD patients or lyophilized pools of plasma distributed by the UK National External Quality Assessment Service (UK NEQAS) were measured repeatedly [3]. Inaccurate measurement of PTH may lead to misclassification of patients and result in inadequate therapeutic decisions [5].

UK National Institute for Health and Clinical Excellence (NICE) guidelines contain recommendations for therapy of sHPT in patients who have either uncontrolled or unresponsive PTH plasma levels and who are not candidate for parathyroidectomy [3]. Therapeutic interventions both from Kidney Disease: Improving Global Outcomes (KDIGO) [6] and Renal Association [7] guidelines recommended PTH recommended target ranges (RTR) for hemodialyzed CKD patients. Novel guidelines replaced the exact numeric values (i.e., 150–300 pg/mL) (K-DOQI, 2003) for RTR to 2ULN and 9ULN (upper level of the healthy normal reference) [6–9]. All these recommendations and guidelines are based on PTH measurements performed with 2nd generation assays are generally referred to as 'intact' PTH assays (iPTH). The limitation of iPTH assays is their cross-reaction with C terminal fragmented (7-84)PTH molecules which may accumulate in patients with CKD [10]. Novel PTH assays referred to as 3rd generation PTH assays [PTH(1-84)] (sometimes also called 'whole' or 'bioactive' PTH assays) have been developed and increasingly recommended for routine diagnostic purposes [6]. These assays exclusively detect the whole (1-84)PTH molecules. While levels measured with iPTH and PTH(1-84) assays generally correlate, PTH(1-84) assays usually provide results 40%–50% lower than iPTH assays [11, 12]. Therefore, reference intervals are affected by these novel assays. However, current guidelines have not fully incorporated this technological development and 3rd generation assays may not be optimal for classification of CKD patients based on current guidelines [13–19].

A PTH standardization meeting in September, 2010 [16] drafted the determination of assay-specific RTR as an outstanding priority in order to select the optimal medical therapy for SHPT in patients with CKD. These recommendations highlighted that switching from one PTH assay to another might be more difficult for PTH than for any other analyte. In order to establish reference values and also RTR values for PTH, samples from healthy, 25-OH-vitamin D-replete individuals are needed.

In the present study we evaluated and compared PTH levels measured by two novel 3rd generation PTH(1-84) assays and three 2nd generation iPTH assays. We compared their classification performance in a hemodyalized CKD population and we implemented a calculation method for determination of RTRs which provided similar classification of patients to those measured with iPTH assay.

Materials and methods

We used plasma samples collected from 110 patients [55 women, 55 men, age: (mean±SD) 56.6±14.7, range: 24–90 years] with CKD on hemodialysis years on treatment: 4.4±4 years (mean±SD).

Determination of PTH levels

Blood was obtained before dialysis sessions in cooled EDTA tubes. Tubes were centrifuged within 30 min of sampling, then aliquoted and stored at −80°C until use. Two 3rd generation assays detecting the whole (1-84)PTH Roche Elecsys PTH(1-84) REF:05608546 190 and Liaison PTH(1-84) REF:13597 and three 2nd generation iPTH assays (Roche Elecsys iPTH REF:11972103 122, Abbott Architect iPTH REF: 8K25 and LIAISON N-TACT PTH II assay REF: 310660) were used. Assay characteristics provided by the manufacturers are summarized in Table 1. All assays were performed according to manufacturers instructions at the Central Laboratory of the Department of Laboratory Medicine, Semmelweis University. This study was approved by the Local Institutional Ethical Committee.

Statistical analysis

Statistical analysis was performed using SPSS v 19. software package. Data are expressed as mean±standard deviation. The comparisons between different groups were performed with Student's paired t-test. Correlations between different PTH assays were determined using parametric Pearson's correlation. A p-value of <0.05 was considered to be significant.

Based on 2ULN and 9ULN of each assays provided by the manufacturers, we classified our patients whether they are below, within or above the PTH RTR. Receiver operating characteristics curve (ROC) was used for calculation of our own RTR for the novel PTH(1-84) assays in order to ensure the classification comparable to that with Elecsys iPTH.

Results

Analytical comparison of different PTH assays

In general, average PTH(1-84) levels for the whole patient group were about 33%–51% lower than iPTH levels were

Manufacturer	iPTH assays			PTH(1-84) assays	
	Elecsys PTH	Architect iPTH	N-tact Liaison PTH	Elecsys PTH(1-84)	Liaison-PTH (1-84)
	REF:11972103 122	REF: 8K25	REF:310660	REF:05608546 190	REF:13597
Method principle	ECLIA	CMIA	CLIA	ECLIA	CLIA
Range of measurement, pg/mL	1.2–5000	3.0–3000	2.0–2000	5.5–2300	1.7–1800
Intra-assay CV, %	1.5–4.1	4.1–9	3.9–6.1	1.6–7.4	≤6
Inter-assay CV, %	2.6–6.5	3–6.4	5.1–8.9	3.1–9.4	≤9
Antibodies used in the assay	Monoclonal mouse (26–32)	Polyclonal goat	Polyclonal goat (1–34)	Monoclonal mouse (54–59)	Polyclonal (C-terminal) Polyclonal (N-terminal)
(amino acid epitopes)	Monoclonal mouse (37–42)	Polyclonal goat	Polyclonal goat (39–84)	Monoclonal mouse (1–5)	
Healthy reference range	15–65	15–68	11.7–61.1	15–57	5.5–38

Table 1 Analytical parameters of PTH assays used.
CLIA, chemiluminescence immunoassay; CMIA, chemiluminescence microparticle immunoassay; CV, variation of coefficient; ECLIA, electrochemiluminescence immunoassay; ULN, upper limit of normal.

[Elecsys PTH(1-84) 149±119 pg/mL and Liaison PTH(1-84) 127±114 pg/mL vs. Elecsys IPTH; 288±247 pg/mL; Architect iPTH 333±278 pg/mL and Liaison N-tact 224.3±203 pg/mL, p<0.001].

Despite these large differences in absolute values strong correlations were detected between each test as R^2 values ranged between 0.76 and 0.981. The lowest R^2 value was obtained when Liaison N-tact assay was compared to others.

Effect of ULNs on classification of CKD patients

Using ULNs provided by the manufacturers, 52.7%–58.2% of patients were within PTH RTR (Table 2). However, a large portion of these patients was not identical.

The next step was to evaluate how switching to the 3rd generation PTH(1-84) assays would affect individual patient's classification. As a result of switching from iPTH

	PTH RTR based on ULNs provided by the manufacturer	Patients number (%) below RTR (<2 ULN of PTH)	Patient number (%) within RTR (2–9 ULN of PTH)	Patient number (%) above RTR (>9 ULN of PTH)
iPTH (2nd generation) assays				
iPTH Elecsys	130–585 pg/mL	30 (27.3%)	62 (56.4%)	18 (16.3%)
iPTH Architect	136–615 pg/mL	25 (22.7%)	64 (58.2%)	21 (19%)
iPTH N-tact Liaison	146–656 pg/mL	40 (36.4%)	63 (57.3%)	7 (6.3%)
PTH(1-84) (3rd generation) assays				
Elecsys PTH(1-84)	114–512 pg/mL	45 (41%)	58 (52.7%)	7 (6.4%)
Liaison PTH(1-84)	77–346 pg/mL	35 (31.8%)	64 (58.2%)	11 (10%)
Number of patients (%) with altered classification when novel PTH(1-84) (3rd generation) assays are used instead of iPTH Elecsys test				
Elecsys PTH(1-84)	114–512 pg/mL	+15 (13.7%)	−4 (−3.7%)	−11 (−9.9%)
Liaison PTH(1-84)	77–346 pg/mL	+5 (4.8%)	+2 (+1.8%)	−7 (−6.3%)
Number of patients (%) with altered classification when novel PTH(1-84) (3rd generation) assays are used instead of iPTH Architect tests				
Elecsys PTH(1-84)	114–512 pg/mL	+20 (18.2%)	−6 (−5.4%)	−14 (−12.7%)
Liaison PTH(1-84)	77–346 pg/mL	+10 (9.1%)	0	−10 (−9.1%)
Number of patients (%) with altered classification when novel PTH(1-84) (3rd generation) assays are used instead of iPTH N-tact Liaison test				
Elecsys PTH(1-84)	114–512 pg/mL	+5 (+4.5%)	−5 (−4.5%)	0
Liaison PTH(1-84)	77–346 pg/mL	−5 (−4.5%)	+1 (+0.9%)	+4 (+3.6%)

Table 2 Classification of chronic kidney disease (CKD) patients based on KDIGO guideline [see ref. [6] in text] using PTH recommended target range (RTR) based on upper limits of normal (ULN) provided by the manufacturers and number of patient misclassified when novel PTH (1-84) are used instead of iPTH assays.

Elecsys to Elecsys PTH(1-84), the PTH of 10% of patients classified originally as above RTR became within RTR and 14% of patients classified originally as within RTR became below RTR. Similar tendencies were observed with any other switch from any iPTH to PTH(1-84) assay (Table 2) except when Liaison PTH(1-84) assay was used instead of Liaison N-tact assay. In this later case only 3.6% of patients were classified differently (Table 2). Using the ULNs provided by the manufacturers the sensitivity of 3rd generation PTH(1-84) assays ranged between 33% and 88.8% (Table 3). Cavalier et al. has published other RTR values for all of the three iPTH assays and for Liaison PTH(1-84), respectively (Supplemental data, Table 1, which accompanies the article at http://www.degruyter.com/view/j/cclm.2013.51.issue-6/issue-files/cclm.2013.51.issue-6.xml). Therefore, we compared how these ULNs would affect the classification of our patients. By using their ULNs the classification showed very similar results to those obtained by using manufacturers' ULNs (Supplementary Table 1, Table 4 and Figure 1).

Determination of novel RTR values

By using ROC curves, we calculated those ULNs that would provide similar classification when PTH is measured by Elecsys PTH(1-84) and Liaison PTH(1-84) assays. We used classification results with Elecsys iPTH test as reference. For both PTH(1-84) assays the calculated ULNs were lower compared to those provided by manufacturers (Table 4). Using our RTR values in all switching types except when Liaison N-tact would be changed to Liaison PTH(1-84), better classification was obtained. In addition, our RTRs performed better than those provided by Cavalier et al (Table 4, Figure 1). However, neither of the Cavalier's RTRs performed well when the switch was from Liaison N-tact to Liaison PTH(1-84) assay.

	Sensitivity with manufacturers' ULN values	Specificity with manufacturers' ULN values	Sensitivity with our calculated ULN values	Specificity with our calculated ULN values
Elecsys PTH(1-84) vs. Elecsys iPTH assay				
2 ULN	80	100	96.3	96.7
9 ULN	39	100	94	100
Elecsys PTH(1-84) vs. Architect iPTH assay				
2 ULN	76.5	100	92	96
9 ULN	33	100	81	99
Elecsys PTH(1-84) vs. Liaison N-tact assay				
2 ULN	93.3	68	86.7	88
9 ULN	100	94	100	98
Liaison PTH(1-84) vs. Elecsys iPTH assay				
2 ULN	88.8	100	96.3	97.3
9 ULN	66.7	98.9	94.4	98.8
Liaison PTH(1-84) vs. Architect iPTH assay				
2 ULN	84	100	91.8	100
9 ULN	57	99	81	98
Liaison PTH(1-84) vs. Liaison N-tact assay				
2 ULN	93.3	68	95	58
9 ULN	100	94.4	100	89

Table 3 At 100% specificity for KDIGO classification, the sensitivity of different PTH(1-84) assays based on manufacturers' ULNs and the specificity and sensitivity of classification using our calculated ULN values, respectively.
ULN, upper limit of normal. 2ULN and 9ULN are discrimination levels recommended by KDIGO guideline.

Discussion

In our current study we modeled a common everyday situation in clinical chemistry when a PTH assay is replaced by another one. We compared the impact of switching on sHPT classification of CKD patients according to the recent KDIGO guideline.

Our results confirmed that iPTH levels measured by Architect are higher than those measured by Elecsys iPTH [20] and that PTH levels measured with 3rd generation PTH assays are about half of those measured with iPTH assays [16, 19]. Using manufacturers' ULNs the clinical classification is altered in up to 23% of CKD patients as the result of switch. However, the Liaison N-tact PTH assay which is a 2nd generation iPTH test showed very similar classification characteristics to those obtained by 3rd generation assays.

Using ROC analysis and using Elecsys iPTH assay as a reference we established the new RTR for PTH(1-84) assays in order to provide the same classification. As any laboratory who intend to switch from one assay to another one has the data already measured, our approach would allow RTRs to be established with similar classification properties to those provided by the prior assay. In our study with these new RTRs the classification based on PTH(1-84) differs just in 1.8%–7.3% of total cases classified according to iPTH levels. Of note, the manufacturer provided RTR for Liaison PTH(1-84) assay resulted in less misclassified patients when the PTH measurement was initially performed with iPTH Liaison N-tact assay. This result may suggest that a smoother switch can be obtained when the newer generation of assays is chosen from the same manufacturer.

It has been demonstrated that the KDIGO guideline using ULNs instead of exact numbers is superior to the earlier K-DOQI guideline where 150 pg/mL, 300 pg/mL and 800 pg/mL iPTH values were defined as therapeutic

	PTH RTR based on our and Cavalier's results	Patients number (%) below RTR (<2 ULN of PTH)	Patient number (%) within RTR (2–9 ULN of PTH)	Patient number (%) above RTR (>9 ULN of PTH)
PTH(1-84) (3rd generation) assays				
Elecsys PTH(1-84) by our RTR	85–258 pg/mL	32 (29%)	55 (50%)	23 (21%)
Liaison PTH(1-84) by our RTR	67–288 pg/mL	33 (30%)	58 (52.7%)	19 (17.3%)
Liaison PTH(1-84) by Cavalier et al.	52–232 pg/mL	20 (18.2%)	62 (56.4%)	28 (25.4%)
Number of patients (%) with altered classification when novel PTH(1-84) (3rd generation) assays are used instead of iPTH Elecsys test				
Elecsys PTH(1-84) by our RTR	85–258 pg/mL	+2 (+1.8%)	−7 (−6.8%)	+5 (+4.8%)
Liaison PTH(1-84) by our RTR	67–288 pg/mL	+3 (+2.7%)	−4 (−3.6%)	+1 (+0.9%)
Liaison PTH(1-84) by Cavalier et al.	52–232 pg/mL	−10 (−9.1%)	0	+10 (9.1%)
Number of patients (%) with altered classification when novel PTH(1-84) (3rd generation) assays are used instead of iPTH Architect tests				
Elecsys PTH(1-84) by our RTR	85–258 pg/mL	+7 (+6.3%)	−9 (−8.2%)	+2 (1.8%)
Liaison PTH(1-84) by our RTR	67–288 pg/mL	+8 (+7.3%)	−6 (−5.4%)	−2 (−1.8%)
Liaison PTH(1-84) by Cavalier et al.	52–232 pg/mL	−5 (−4.8%)	−2 (−1.8%)	+7 (+6.3%)
Number of patients (%) with altered classification when novel PTH(1-84) (3rd generation) assays are used instead of iPTH N-tact Liaison test				
Elecsys PTH(1-84) by our RTR	85–258 pg/mL	−8 (−7.3%)	−8 (−7.3%)	+16 (15.5%)
Liaison PTH(1-84) by our RTR	67–288 pg/mL	−7 (−6.3%)	−5 (−4.8%)	+12 (+11%)

Table 4 Classification of chronic kidney disease (CKD) patients based on KDIGO guideline using PTH recommended target range (RTR) based on upper limits calculated by receiver operator characteristics (ROC) analysis and based on data provided by Cavalier et al. [see ref. [19] in text] and number of patients misclassified when novel PTH (1-84) are used instead of iPTH assays.

decision points [17]. The benefit of KDIGO guideline is the minimization of discrepancies resulting from the analytical performances of different assays and the establishment of assay-independent therapeutic decision limits. Our RTR for Liaison PTH(1-84) assay is comparable to those published by Cavalier et al. in a healthy population [19], and is close to that of Ca-PTH(1-84) IRMA assay. RTR for Liaison and Elecsys PTH(1-84) assays in our study were 65 and 68 pg/mL, and 258 and 288 pg/mL, vs. previously published 52 pg/mL and 62 pg/mL, and 232 pg/mL and 277 pg/mL, respectively. These results confirm that the RTR suggested by KDIGO guideline cannot be calculated from those ULN that manufacturers provide as a reference range for PTH(1-84) levels.

Any switch between PTH assays should be performed carefully. Additionally, to the analytical validation the

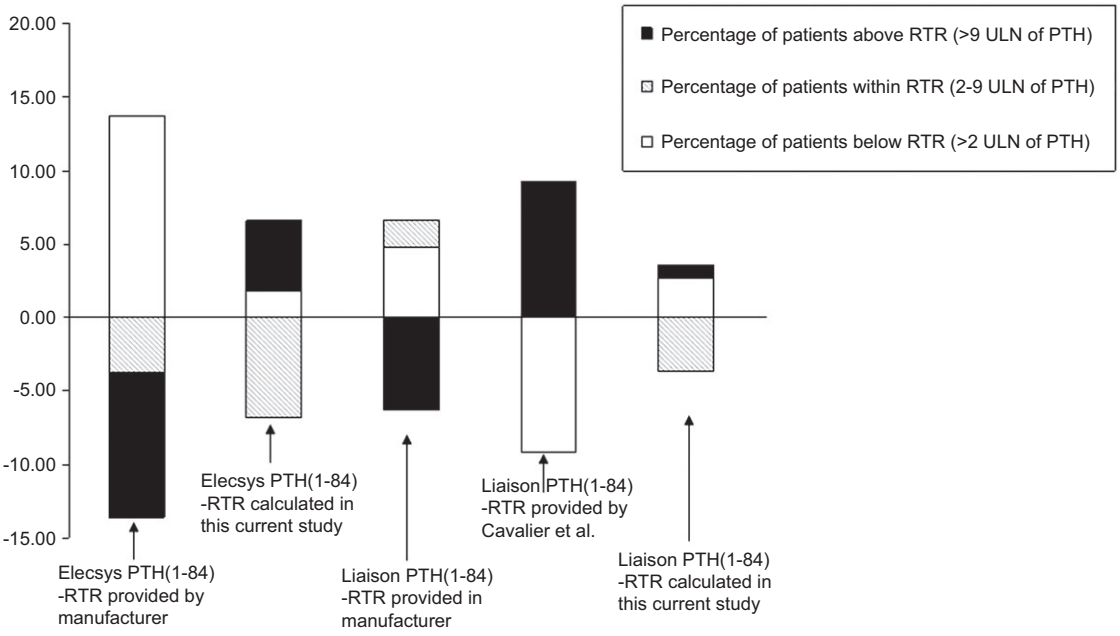

Figure 1 Percentage of patients misclassified when novel PTH(1-84) assays are used instead of Elecsys iPTH.

laboratory should establish its own RTR used for clinical decision-making in CKD. Our analysis highlights that RTR based on ULNs provided by manufacturers is insufficient for this purpose as it may lead misclassification in a significant portion of patients, if earlier iPTH assays are used as reference.

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