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Intact Parathyroid Hormone: Performance and Clinical Utility of an Automated Assay Based on High-Performance Immunoaffinity Chromatography and Chemiluminescence Detection

David S. Hage,1 Bob Taylor,2 and Pal C. Kao2

The performance and clinical utility of an automated assay of intact parathyroid hormone (parathyrin, PTH) are evaluated. The method is based on the extraction of PTH from plasma by an HPLC column containing immobilized anti-(44–68 PTH) antibodies. The PTH retained is detected with a postcolumn reactor and use of anti-(1–34 PTH) chemiluminescent-labeled antibodies. The total cycle time of the assay is 6.5 min per injection after a 1-h incubation. The lower limit of detection for PTH in a 66-μL plasma sample was 0.5 pmol/L based on peak heights and 0.2 pmol/L based on peak areas. Mean analytical recovery for PTH added to plasma was 97%. The within-day precisions (CVs) for 4.2 and 30 pmol/L PTH plasma samples were 9.2% and 5.6% and the day-to-day precisions were 10.3% and 5.7%, respectively. No significant interferences from 1–34, 44–68, or 53–84 PTH fragments were noted, even at highly increased concentrations of fragments. The correlation of results with those of a manual assay of intact PTH was 0.97, and the results showed good agreement with disease state for patients with hypo- or hyperparathyroidism. The specificity of the assay for primary hyperparathyroidism was >95%. We discuss the advantages (speed and quality control) of this approach over current immunoassays and the potential use of this method for detecting other analytes.

Additional Keyphrases: hyperparathyroidism • chronic renal failure • hypercalcemia of malignancy

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3 Nonstandard abbreviations: BSA, bovine serum albumin; HPLAC/CL, high-performance immunoaffinity chromatography with chemiluminescence detection; ICMA, immunochemiluminescent assay; and PTH, parathyrin (parathyroid hormone).

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The measurement of parathyrin (parathyroid hormone; PTH), an 84-amino-acid peptide produced by the parathyroid glands, is a useful tool in the diagnosis of calcium disorders.3 The main function of PTH is to control the concentration of calcium in extracellular fluids, with the excretion of PTH increasing as the calcium concentrations decrease (1, 2). Normal concentrations of intact PTH in plasma range from ~1 to 5 pmol/L, with both the increased and decreased values being of clinical interest (2, 3). Besides intact PTH, various fragments representing the N-terminal, mid-molecule, and C-terminal regions of PTH are also found in blood. Most of these fragments are formed after release of intact PTH into the circulation, but some are also produced within the parathyroid glands (4). Both intact PTH and its N-terminal fragment are biologically active, with intact PTH being the predominant active form under normal conditions (2).

PTH assays are used clinically in the differential diagnosis of disorders that produce hypercalcemia or hypocalcemia (e.g., primary hyperparathyroidism or hypercalcemia of malignancy) and in monitoring bone damage in patients with chronic renal failure (1, 2). The pathology and clinical importance of these disorders have been previously discussed (1–6).

Numerous methods are available for the clinical measurement of PTH in these disorders. These are typically based on immunoassays with antibodies directed toward the N-terminal, midmolecule, or C-terminal regions of PTH. One factor complicating the use and comparison of these assays is that they have different degrees of response to intact PTH and its circulating fragments (1–2). Several methods for monitoring only intact PTH were recently reported, based on two-site immunoassays (7–9). In these assays two sets of antibodies are used: one set is immobilized onto a solid support and...
used to bind one end of intact PTH, such as its 1–34 N-terminal region; the second set is labeled and used to identify the presence of PTH by binding to a second domain, such as the 44–68 midmolecule region. Given this combination, only intact PTH will react with both sets of antibodies and be detected (7–9).

Routine monitoring of intact PTH is best done with a method that is not only sensitive but also fast and fully automatable. However, current intact PTH assays are manual methods that take a long time to perform (i.e., typically 24 h). To overcome these problems, we (10) recently developed an automated system for intact PTH, based on high-performance immunoaffinity chromatography and chemiluminescence detection (HPIAC/CL).

In this method, PTH plasma samples are first incubated with acridinium ester-labeled anti-(1–34 PTH) antibodies. This mixture is then injected onto a column containing anti-(44–68 PTH) antibodies immobilized to a small-particle, silica-based support. The immobilized antibodies extract from the sample any intact PTH present, along with its associated labeled antibodies. After nonretained components and excess labeled antibodies are washed from the column, a low pH buffer is applied to elute intact PTH and its associated labeled antibodies from the column. As these compounds are sluted, they are combined on-line with an alkaline peroxide postcolumn reagent; the resulting production of light from the acridinium ester label is measured with a flow-through detector. The column is then regenerated, and the next sample is injected (10).

In a previous report we described the design and optimization of this system for PTH determinations (10). Here we examined the performance and utility of this method in a routine clinical setting: we considered the response, precision, and accuracy of the method and the effects of potential interferences, such as circulating PTH fragments. We also examined how this method correlated with manual PTH immunoassays and compared the results of this technique for patients with hyper- and hyperparathyroidism with those obtained for normal individuals. The potential advantages and limitations of this method in the automation of immunoassays of PTH and other compounds are discussed.

**Materials and Methods**

**Reagents**

The 1–34, 1–44, 44–68, and 56–84 fragments of human PTH and 1–84 intact human PTH were obtained from Peninsula Labs. (Belmont, CA). The cyanogen bromide-activated Sepharose 4B, goat IgG, and bovine serum albumin (BSA; RIA grade) were from Sigma Chemical Co. (St. Louis, MO). Triton X-100, electrophoresis grade, was from Fisher Scientific (Fair Lawn, NJ). 1-(2-Succinimidyloxybenzoyl)-phenyl-10-methyl-acridinium-9-carboxylate fluorosulfonate (i.e., acridinium ester) was from London Diagnostics (Eden Prairie, MN). The Nucleosil SI-1000 (7-μm particle diameter, 100-nm pore size) was obtained from Alttech Associates Deerfield, IL). The 0.25-in. (6.3-mm) polymeric beads used in the immunochemilumimetric assay (ICMA) were from Micromembranes, Inc. (Newark, NJ). All solutions were prepared with water from a Milli-Q Water System (Millipore, Bedford, MA).

**Instrumentation**

The chromatographic system was the same as described before (10). We used a Hitachi (Tokyo, Japan) L-6200 ternary pump for mixing and pumping postcolumn reagent and two Hitachi L-6000 isocratic pumps for delivering the application and elution buffers to the immunoaffinity column. Samples were injected with a Hitachi 655A-40 autosampler. Components leaving the immunoaffinity column in the elution buffer were detected on-line with an 825-CL chemiluminescence detector (Jasco, Easton, MD). The application and elution buffers were applied alternately to the immunoaffinity column through a column-switching system consisting of a Rheodyne 5701 tandem enrichment valve and a Vici DVI actuator (Chromtech, Apple Valley, MN), controlled from the L-6200 pump. The data were collected and processed by a Hitachi D-2500 Chromatointegrator.

**Procedures**

Anti-(1–34 PTH) antiserum was prepared in goats by using BSA-conjugated 1–44 PTH as the initial immunogen, followed by later injections of unconjugated 1–44 PTH. Before use, these antibodies were affinity-purified in columns containing 1–34 PTH fragments immobilized onto a 7 mm (i.d.) × 15 cm cyanogen bromide-activated Sepharose 4B column (10).

Anti-(44–68 PTH) antiserum was prepared by injecting goats with BSA-conjugated 44–68 PTH. The anti-(44–68 PTH) antibodies were also affinity-purified, with use of 44–68 PTH fragments immobilized onto a 7 mm (i.d.) × 15 cm cyanogen bromide-activated Sepharose 4B column (10).

The anti-(1–34 PTH) antibodies were labeled with acridinium ester and purified on a 7 mm (i.d.) × 15 cm 1–44 PTH cyanogen bromide-activated Sepharose 4B affinity column as described previously (11). Active labeled antibodies collected from the affinity column were diluted in 0.10 mol/L phosphate buffer, pH 7.4, containing 1 g of BSA, 1 g of goat IgG, and 1 mL of Triton X-100 per liter, then stored at −20 °C until required for further use.

The manual ICMA assay used in the correlation studies was performed as described previously (9). The acridinium ester-labeled anti-(1–34 PTH) antibodies were the same as used with the HPIAC/CL system. The beads bearing immobilized antibody were prepared by attaching the affinity-purified anti-(44–68 PTH) antibodies to the polymeric beads, according to the manufacturer's instructions. At the end of the assay, we measured the chemiluminescence of the beads by using a Magic Lite Analyzer (Ciba Corning, Medfield, MA).

**Chromatography**

The immunoaffinity column was prepared as described previously (10), by using affinity-purified anti-(44–68 PTH) antibodies immobilized onto diol-bonded
Nucleosil Si-1000 silica. Using the bicinchoninic acid protein assay (12), we estimated that 1.4 mg of antibodies per gram of silica was immobilized onto the support.

The anti-(44-68 PTH) Nucleosil support was downward slurry-packed at 25 MPa into 4.0 mm (i.d.) × 2.0 cm stainless steel columns from Upchurch (Oak Harbor, WA). Samples were injected onto the column in 0.10 mol/L potassium phosphate buffer, pH 7.4, containing 1 mL of Triton X-100 and 1 g of BSA per liter. The retained PTH was eluted with pH 3.0 potassium phosphate buffer (0.10 mol/L), containing Triton X-100, 1 mL/L. All chromatography was performed at room temperature.

PTH standards were prepared by adding 1–84 human PTH to EDTA-treated plasma collected from patients with hypoparathyroidism and having no endogenous PTH production. For analysis, we mixed 200 μL of each plasma sample with 100 μL of a 50-fold dilution of the acridinium ester-labeled antibodies in phosphate buffer (0.10 mol/L, pH 7.4) containing 1 mL of Triton X-100, 1 g of BSA, and 1 g of goat IgG per liter. The samples were then filtered through 0.45-μm pore size ACRO LC13 disposable filters (Gelman Sciences, Ann Arbor, MI) and incubated in the autosampler tray of the HPLC at room temperature for at least 1 h. We then injected 100 μL of sample onto the HPIAC/CL system at a flow rate of 1.0 mL/min. We used the following event schedule in each chromatographic analysis: 0.0 min, switch column to pH 7.4 phosphate buffer and allow column to regenerate; 1.0 min, inject sample and wash nonretained components and excess labeled antibody from the column; 3.0 min, switch to pH 3.0 phosphate elution buffer and detect the PTH and associated labeled antibodies; 6.5 min, begin next cycle.

Retained PTH and associated labeled antibodies were detected as they eluted from the column by combining the column eluent with a postcolumn reagent containing, per liter, 10 mL of Triton X-100, 0.75 mol of sodium hydroxide, and 0.43 mmol of hydrogen peroxide. This reagent was prepared on-line, as described previously (10), and was applied to the system at a flow-rate of 1.0 mL/min. The post-column reagent and column eluent were combined by using a standard mixing tee from Upchurch. The mixture was then immediately passed through the flow cell of the on-line chemiluminescence detector, and the light produced by the acridinium ester label was monitored.

Subjects

Normal PTH samples were obtained by collecting EDTA-treated plasma from 45 healthy volunteers between ages 20 and 60 y. These volunteers were laboratory technicians and individuals participating in a study to determine normal values. All normal subjects had total serum calcium concentrations between 2.13 and 2.50 mmol/L (mean 2.29 mmol/L).

EDTA-treated plasma samples were also obtained from 46 patients with surgically confirmed primary hyperparathyroidism. These samples were collected before removal of the affected parathyroid glands. The mean total serum calcium in these patients was 2.80 mmol/L (range 2.50–3.23). The mean serum creatinine and inorganic phosphorus concentrations in these patients were 85 μmol/L (range 44–230) and 0.89 mmol/L (range 0.58–1.26), respectively.

EDTA-treated plasma samples were collected from 40 patients with chronic renal failure. Their mean total serum calcium concentration was 2.41 mmol/L (range 1.48–2.90), mean serum creatinine was 710 μmol/L (210–1200), and mean inorganic phosphorus was 2.27 mmol/L (range 1.07–5.78).

EDTA-treated plasma samples were obtained from 36 individuals with hypercalcemia of malignancy. The following types of malignancies were represented: squamous cell carcinoma (n = 8), lymphoma (n = 6), breast cancer (n = 4), renal cell carcinoma (n = 4), multiple myeloma (n = 4), prostate cancer (n = 2), sarcoïdosis (n = 2), and 1 each of small cell carcinoma, islet cell carcinoma, lung adenocarcinoma, hemangioepicytoma, dysgerminoma, ovarian tumor, paraganglioma, and grade 4 adenocarcinoma with an unknown primary origin. The mean total serum calcium in these patients was 3.23 mmol/L (range 2.83–3.96). Their mean serum creatinine and inorganic phosphorus concentrations were 130 μmol/L (range 60–410) and 1.01 mmol/L (range 0.58–1.58), respectively.

Results

Assay Performance

The carryover of the HPIAC/CL system was <0.16%, as determined by making several alternate injections of 1000 and 0 pmol/L PTH plasma standards. On the basis of these carryover studies and previous work, we developed the event schedule given in Materials and Methods. With this scheme, the total chromatographic time was only 6.5 min per injection, following a 1-h incubation of sample with labeled antibody. Earlier studies have shown that most (>70%) of the PTH and labeled antibodies bind within this incubation time (10); consequently, even samples that are incubated for >1 h before injection present only slight variations in the final signal produced with this system.

Under the above chromatographic conditions, the minimum turnaround time per sample was ~1 h, including the time required for sample preparation, incubation, injection, and analysis. Given a chromatographic time of 6.5 min per sample, the theoretical throughput of this system is 220 samples per day. In practice, an average calculated throughput of 180 ± 20 samples per day (n = 19 days) has actually been obtained.

Typical chromatograms obtained with the HPIAC/CL system are shown in reference 10. An example of the calibration curve generated with this system is shown in Figure 1. These results were obtained by injecting a single set of plasma standards onto the system. To quantify the amount of PTH represented by each peak, one can use either peak heights or areas. Based on multiple injections of low-concentration PTH standards, the lower limit of detection at a signal-to-noise ratio of 3.
was determined as 0.2 pmol/L for peak-area measurements and 0.5 pmol/L for peak-height measurements. These limits of detection reflect the concentration of injected PTH required to produce a signal 2 SD above the signal produced by the zero standard and agree with previous data obtained with this system (10).

As shown in Figure 1, the linear range (i.e., the range of concentrations within ±5% of the best-fit line) extended up to 38 pmol/L for the peak-height measurements. For peak-area measurements, the same standards demonstrated a linear range extending to 44 pmol/L. Thus, the peak-height and peak-area calibration curves had linear ranges for concentrations covering 1.8 and 2.3 orders of magnitude, respectively. These results also agree with earlier work on this system (10) and are similar to linear ranges seen for manual PTH assays. The dynamic range (i.e., the range of concentrations producing any detectable change, linear or nonlinear, in the response) extended up to at least 250 pmol/L, with no apparent hook effect.

Analytical recovery of intact PTH in the HPIAC/CL system was determined by analyzing normal plasma samples supplemented with various amounts of exogenous intact PTH. As Table 1 illustrates, all samples showed a high degree of recovery, with values ranging from 93% to 102% (mean 97%).

Table 1. Analytical Recovery of Intact PTH on the HPIAC/CL System

<table>
<thead>
<tr>
<th>PTH conc, pmol/L</th>
<th>Endogenous</th>
<th>Added</th>
<th>Recovered*</th>
<th>Recovery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>3.1</td>
<td>5.5</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>7.3</td>
<td>9.5</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>19.9</td>
<td>20.8</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>3.4</td>
<td>3.7</td>
<td>6.7</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>3.4</td>
<td>6.8</td>
<td>10.4</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>3.4</td>
<td>10.5</td>
<td>13.8</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

* Results shown are for single sample injections.

Parallellism of the HPIAC/CL system was assessed by measuring intact PTH in a series of dilutions prepared from plasma samples with above-normal concentrations of PTH. The data for all diluted samples showed excellent agreement with the results predicted from the original sample (Table 2). For the first sample, the average relative error was only −0.6% (range −2.6% to +1.6%); for the other sample, the average relative error was +1.0% (range −4.1% to +8.2%).

The within-day precision of the automated PTH assay was measured by making 20 sequential injections of plasma samples with either normal or abnormal concentrations of PTH (4.2 and 30 pmol/L, respectively). The within-day precisions (CVs) for these samples were ±9.2% and ±5.6%, respectively. The day-to-day precision of the system was determined by injecting the same samples over the course of 10 d. The day-to-day precision was ±10.3% for the normal samples and ±5.7% for the abnormal samples. All of these results are similar to those obtained with equivalent manual PTH immunoassays (7, 8).

The immobilized antibody solid-phase used in this work was stable for several months when stored at 4 °C in pH 7.0 phosphate buffer. When the support was placed in a column, typical column lifetimes of 200–250 plasma injections were obtained (mean 230, SD 30, for three columns). This column life is similar to that seen for other antibodies immobilized to silica (13–16) and indicates that the system was sufficiently stable for performing many analyses of patients' samples.

As shown previously, little or no change in the activity of the immobilized antibody was found under the elution conditions used in the HPIAC/CL system (10). Measuring the total binding capacity of the immobilized antibody support over multiple elution cycles had shown that the total binding capacity of the column for 44–68 PTH decreased by <0.3% with each elution cycle (10). In this study, we further examined column stability by comparing a series of five calibration curves obtained over a series of 143 injections with use of a single column and a single labeled-antibody preparation. Al-
though some random variation was noted between the individual calibration curves, linear regression of the slopes and intercepts indicated no significant change (<8%) in the curves over the course of this study, whether based on peak heights or peak areas. From this we concluded that the stability of the immobilized antibody was not a major factor in limiting the column life.

One important factor affecting column life was a buildup in pressure after a large number of plasma samples were injected. To reduce this pressure increase, we implemented several precautions throughout this study, such as filtering all samples before injection and placing a precolumn filter in the system to prevent particulate matter from reaching the immobilized-antibody column. Changes in the pressure of the system during the application and elution steps were also monitored for quality control. Pressure monitoring was useful because it indicated when and where pressure was increasing and what type of corrective action was needed. Typical sources of pressure increases were the precolumn filter and column. To minimize these increases in routine testing, we replaced the filter in the precolumn filter after every 100 injections and changed the column after every 200 injections.

To determine the correlation of the HIPIA/CL system with a manual intact PTH assay, we used both procedures to analyze a series of 130 patients' samples in which intact PTH concentrations ranged from 0.5 to 42 pmol/L. The best-fit line between the results of the two assays (Figure 2) had a slope (± 2 SD) of 0.99 ± 0.04 and an intercept of 0.70 ± 0.6 pmol/L; the correlation coefficient was 0.97.

Clinical Utility and Interference Studies

Figure 3 shows the results obtained with the HIPIA/CL system for single determinations of normal plasma samples and samples obtained from patients with primary hyperparathyroidism, chronic renal failure, or hypercalcemia of malignancy. For the 45 normal samples tested, the mean concentration of intact PTH was 2.2 pmol/L; the total range of concentrations observed was 0.6–5.6 pmol/L. Using nonparametric analy-

![Figure 2](image)

Fig. 2. Correlation of HIPIA/CL with a manual intact PTH immunochemistry assay (ICMA). Best fit line: \( y = (0.99 ± 0.04)x + (0.7 ± 0.6) \), corr. coef. = 0.97, \( n = 130 \)

![Figure 3](image)

Fig. 3. Plasma concentrations of intact PTH measured by HIPIA/CL in normal individuals and in patients with hypercalcemia of malignancy (HM), primary hyperparathyroidism (1.7 HPT), or chronic renal failure (CRF)
In these studies, we noted no detectable interference in either the 0 or 5 pmol/L PTH samples at concentrations as great as 30 nmol/L for 53–84 PTH or 20 nmol/L for 44–68 PTH. No interference from 1–34 PTH was seen for a fragment concentration as great as 250 pmol/L. These quantities of fragments exceed the concentrations seen in most clinical situations, including chronic renal failure, and indicate that little interference would be expected from these fragments in routine testing. The 1–34 PTH results also suggest that this assay would have little or no interference from PTH-related peptide, which has its greatest structural homology with PTH in the 1–13 N-terminal region (17).

Discussion

This study demonstrates that HPIAC/CL is a useful approach to the routine analysis of intact PTH. Not only is the method fully automatizable, but it also has provisions, limits of detection, and results comparable with those of current PTH assays. This development is important because no fully automated method for PTH has previously been reported.

One key advantage of this method is that its overall analysis time (i.e., 1 h per sample) is significantly shorter than that reported for comparable manual PTH assays. For example, Nussbaum et al. (8) reported a 24-h immunoradiometric assay for quantifying intact PTH in 200 μL of serum; its limit of detection was ~0.1 pmol/L. Brown et al. (9) reported a 5-h manual ICMA for 100-μL samples, with a limit of detection of 0.8 pmol/L.

One reason for the greater speed of this method is the much larger excess of antibody used in the HPIAC/CL system than is typically present in a manual immunoassay support. This allows for more rapid binding between the immobilized antibody and the PTH-labeled-antibody complex. The support used in the HPIAC/CL system is also much smaller than that used in manual immunoassays; this results in faster mass transfer and also provides for more rapid extraction of the PTH-labeled-antibody complex. In previous studies (10), we showed that the combination of these two factors produced a net rate of extraction of PTH and its associated labeled antibody ≈2400-fold faster than that for the same sample and antibodies used with a standard immunoassay bead.

This HPIAC/CL method is not limited to PTH but can be adapted to detect other compounds by using different labeled antibodies and columns. Such an approach should be particularly useful in analyzing other low-concentration peptide hormones for which automated systems are not available (e.g., calcitonin and corticotropin). We are also examining the use of HPIAC/CL to determine smaller molecules.

One potential advantage of HPIAC/CL over existing methods for PTH is that it analyzes samples sequentially rather than in a batch mode. This should make HPIAC/CL potentially easier for troubleshooting and maintaining quality control. For example, if the result for a control sample is outside its allowed limits with HPIAC/CL, it is relatively easy to change the column or buffers and recheck the control without wasting a substantial amount of time before patients’ samples are tested. In contrast, the long analysis times of manual PTH methods means that controls and samples must be analyzed simultaneously. This creates a problem if the results for the controls are later found to be outside acceptable limits, because diagnosing and fixing the problem may take several days. This increases time and cost because the patients’ samples must be redetermined.

The fast analysis times of HPIAC/CL make it attractive to use for rapid determinations of individual samples or for small-scale routine analysis. For situations requiring throughput of several hundred samples per day, either multiple HPIAC/CL systems or batch-mode manual immunoassays are recommended.

In summary, HPIAC/CL is an attractive alternative to manual methods for determining intact PTH in plasma. This method has the advantages of being both fast and fully automatizable, while retaining the accuracy, precision, and response of manual PTH assays. In addition, HPIAC/CL has the potential of being more cost-effective and of maintaining quality control more easily than present batch assays. All of these characteristics make this approach appealing for use in the routine monitoring of intact PTH and other low-concentration analytes.

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