Recommendations from the Working Group of Senior Scottish Clinical Biochemists on Parathyroid Hormone (PTH) Targets in the Management of Renal Failure

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1. Background

1.1. The chairman of the group (SW) is the laboratory representative on the Scottish Renal Registry (SRR) and had been asked by the chairman and members of the SRR to comment on PTH, calcium, phosphate and albumin data collection issues for a planned SRR audit in this area. This highlighted the question of comparability of PTH data across the different renal units in Scotland, depending on the local assay which serves these units. It also raised secondary questions as to sample collection requirements for PTH and reporting units.

1.2. In addition to concerns over PTH data comparability, questions were also raised as to nature of the albumin assay used and whether the total calcium measurement was corrected for albumin concentration. If a correction was used, a further question was the nature of the correction formula.

1.3. In order to address these problems on behalf of the SRR, SW raised the possibility of setting up a working group at a meeting of Senior Scottish Clinical Biochemists organised by Ian Gunn (Wishaw) in Autumn 2007. The wide representation at this meeting made it possible to support a Scotland-wide initiative under the chairmanship of SW with good representation across Scotland. This group (hereafter referred to as the "PTH working Group") met on two occasions to clarify the problems to be examined; decide on what information was required to be collected to inform the decision-making; issue recommendations arising from this work. This document explains the nature of the problem, with particular regard to PTH measurement, and establishes a set of proposals for adoption throughout Scottish Clinical Biochemistry Laboratories. The proposals impact on the work of renal units in Scotland and have the full support of the SRR.

2. The Problem

2.1 There are five different PTH assays which serve the renal units in Scotland. In the absence of an agreed international PTH standard

assay comparability is a problem. In particular, UK NEQAS data shows that there is a wide method-dependent bias around the All Laboratory Trimmed Mean (ALTM) which is, nevertheless, precise. Moreover, a range of values for the upper limit of the reference range is used which fails to reflect the method bias. The problem is compounded by over-recovery of synthetic PTH_{1-84} and method-dependent differences in sensitivity towards PTH_{7-84}.

2.2 Despite the assay bias differences, which are not reflected in the upper limit of the reference range, all the Scottish renal units work towards the same PTH target which is 2 - 4 x upper limit of the reference range. The origin of this particular target is discussed in more detail in Paper 1.

2.3 The consequence is that patient management, using the agreed PTH target, is not comparable across the different renal units. Some units are likely to be under-treating and others over-treating, based on this target.

2.4 Laboratories across Scotalnd that measure PTH also use two different units. At the time of writing, there are eight laboratories which use pmol/L and six which use ng/L. It should be noted that, whilst these are the units used to report to UK NEQAS, it is possible that some laboratories report to users in a different unit to that used for the UK NEQAS reporting.

2.5 For the range of assays used in Scotland, the manufacturers also make variable recommendations as to the sample collection requirements.

2.6 The group also reviewed the arrangements across the Scottish laboratories for measuring albumin and reporting total calcium and corrected calcium. Up-to-date information was agreed to be required as to which methods for calcium, albumin and phosphate are in use across Scotland; whether the total calcium is corrected for albumin; the nature of any correction formula used; whether there is a lower limit for albumin reporting and a cut-off for albumin when the correction is not then applied.

3. Plan of Action

3.1 A key question is how the different PTH assay results compare on samples from patients with chronic renal failure. To address this question, an initial exchange of 20 or so samples from patients with chronic renal failure was undertaken. The 20 samples were collected by KS and dispatched to AE at UKNEQAS. AE aliquoted the samples, froze them and, on an agreed date, sent an aliquot from each specimen to 5 Scottish laboratories. Each laboratory was selected for the reason that it uses one of the 5 different PTH assays in use in Scotland. This preliminary data made it clear that

it would be important and worthwhile to extend the assay comparison by increasing the sample number to over 100. For this purpose, EDTA plasma was obtained that was surplus to routine analytical requirement (by KS from Glasgow Royal Infirmary). Plasma obtained from these patients with chronic renal failure was again aliquoted and despatched by AE. The PTH results were returned to UK NEQAS for further analysis.

3.2 The results of the method comparison are discussed in detail in the attached Paper 1. In summary:

- For each specimen the overall mean ('target') was calculated as the mean of the results from the 5 methods (equivalent to the UKNEQAS ALTM).
- Each result for each specimen was then expressed as a percentage deviation (bias) from the 'target' value.
- For each method, the mean of the BIAS for all the specimens analysed by that method was calculated (equivalent to UKNEQAS method mean bias).

3.3 In addition to the PTH sample exchange, KS also agreed to re-audit the Scottish laboratories to determine which methods are used for measurement of calcium, albumin and phosphate. At the same time, information was requested on the calcium reference range used, whether a correction for albumin was applied and the nature of that correction. Further questions related to the lowest level of albumin reported and whether the calcium correction was not applied below a specified albumin cut-off. The audit is summarised in Paper 2.

3.4 Using the findings from the PTH sample exchange and the calcium, albumin and phosphate audit findings, the PTH Working Group makes a number of proposals to achieve better comparability of PTH control at the different renal centres and better agreement in the way in which calcium and albumin results are reported across Scotland. These proposals are covered in the next section.

4. **Proposals**

4.1 Based on stability information on PTH in EDTA plasma and the fact that all current assays support this matrix, the PTH Working Group proposes that all PTH assays in Scotland be measured on EDTA plasma. Recent work from SW's laboratory (unpublished) has also made it clear that, for at least one PTH assay manufacturer, it is critical to provide an adequately filled EDTA sample tube to obtain a meaningful result (underfilling leads to artefactually low values).

4.2 To unify reporting arrangements, the PTH Working Group further recommends that the units of PTH reporting should be pmol/L.

4.3 Using the results of the 100 sample exchange from patients with chronic renal failure, it was possible to obtain a clear picture of the relative bias differences of the different PTH assays in serum from patients with renal failure. From this information, assay-specific targets for PTH levels in patients with chronic renal disease are proposed. These assay-specific targets are recommended to be adopted by each renal unit in accordance with the particular PTH assay used by that unit. Although the targets differ between PTH assays, this approach will achieve much greater comparability of PTH control than is the case at present. This is reflected in the fact that the two assays showing the extremes of bias difference from the patient exchange (Diasorin Liaison and Siemens Immulite 2000) have targets which are almost 2-fold different. The alternative approach of adjusting each PTH assay result within the laboratory and all the renal units then working to the same target was felt to be unsatisfactory for a number of reasons, including:

- Resistance to adjusting individual PTH assay results on theoretical and practical grounds.
- Uncertainty in returning external QC PTH results to UK NEQAS.
- Concerns over the effect of adjusting PTH values on samples from patients without renal failure.

The basis for the assay-specific targets is detailed in Paper 1a which also provides some background as to how the original PTH target was arrived at.

4.4 The recommended targets are as follows:

Abbott Architect	16 - 31 pmol/L
Beckman Access DxI	13 - 25 pmol/L
DiaSorin Liaison	12 - 24 pmol/L
Roche Elecsys	14 – 28 pmol/L
Siemens ADVIA Centaur	15 - 31 pmol/L
Siemens Immulite 2000	22 - 45 pmol/L

4.5 These arrangements should be regarded as interim. Once an international standard for PTH is agreed and the different assay manufacturers calibrate against the agreed international standard, it is anticipated that the assay bias differences should decrease. This is likely to improve PTH assay comparability and ultimately allow the adoption of a single PTH target by all renal units.

4.5 The patient sample exchange data showed that assay bias differences parallel those found for UK NEQAS distributions which include plasma from patients with chronic renal failure. Accordingly, UKNEQAS will continue to monitor all the PTH assays in use in Scotland and keep under review the assay-specific PTH targets proposed.

4.6 With regard to the adjustment of total calcium measurements for

albumin, there were seven different formulae in use which differ very little from one another. The PTH Working Group recommends that all laboratories provide a corrected calcium using a single adjustment which is the 40/0.02 formula as detailed in Paper 2. It is further proposed that the adjustment formula only be applied for albumin levels of 25 g/L or more.

4.7 Albumin levels which are below 10 g/L should not be reported as absolute values but as <10 g/L.

4.8 A final recommendation is that adjustment of neonatal calcium results is not supported.

SUMMARY of RECOMMENDATIONS

- Adopt assay specific PTH targets for patients with chronic renal failure until an international standard is available for calibration
- Use EDTA plasma as the preferred sample for PTH measurement and report results in pmol/L. Specimen containers must be properly filled.
- Adopt a common adjustment formula of (40-albumin)x0.02, to be applied if albumin >25g/l
- Do not adjust neonatal calcium
- Report low serum albumin as <10g/l
- Adopt common Scotland-wide reference ranges for calcium, phosphate, albumin and total protein

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