Establishing a practical blood platelet threshold to avoid reporting spurious potassium results due to thrombocytosis

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Abstract

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Background: Thrombocytosis is one of several pre-analytical factors which contribute to spuriously high serum potassium concentrations, yet there is little published data to guide analysts in the selection of a specific platelet count threshold above which serum potassium results become unreliable. We have studied the sensitivity and specificity of blood platelet count as a predictor of false elevations in potassium.

Methods: Paired serum and plasma potassium measurements together with full blood count were performed for 300 patients. All samples were stored at room temperature and analysed within 4 h of collection. The difference between serum and plasma potassium was plotted against blood platelet count.

Results: When the difference (serum-plasma) in potassium concentration was plotted against platelet count, there was a direct linear relationship. Blood platelet counts of $> 500 \times 10^9/L$ will detect elevations in serum relative to plasma potassium of $> 0.5 \text{ mmol/L}$, with a sensitivity of 71% and a specificity of 89%.

Conclusion: It is recommended that where blood platelet count is above $500 \times 10^9/L$, potassium measurements should be repeated using lithium heparin plasma. When serum potassium results of $> 5.4 \text{ mmol/L}$ are obtained, it is our policy to check the platelet count if a sample is available before reporting results. If available and above $500 \times 10^9/L$, potassium results are withheld and plasma requested.

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Background

Pseudohyperkalaemia is defined as high measured serum potassium in the presence of normal *in vivo* plasma potassium confirmed by normal measured plasma potassium levels. It has become well recognized that attention to sample collection and handling is crucial to successful serum potassium measurement. Haemolysis, delay in centrifugation, refrigeration of blood before centrifugation, fist clenching during phlebotomy, leucocytosis and even seasonal ambient temperature variation¹ have been documented as causes of factitious hyperkalaemia.

High blood platelet count (thrombocytosis) is another pre-analytical factor known to cause pseudohyperkalaemia. There are many published case reports

which document this.^{2–4} A large retrospective study⁵ has also shown a relationship between serum potassium and platelet count.

There is, however, little guidance for analysts to indicate the platelet threshold above which potassium results should be regarded with suspicion. The authors' laboratory has been routinely withholding elevated serum potassium results ($> 5.4 \text{ mmol/L}$) where blood platelet count was $500 \times 10^9/L$ or above and requesting lithium heparin samples. This platelet count threshold was based mainly on observation and it was decided to carry out a formal evaluation to validate its selection and to investigate the magnitude of the elevations obtained at various platelet counts. We have found only one other study where potassium was measured in paired serum and plasma samples for a large patient

group together with full blood count.⁶ That work included 91 subjects with high platelet counts and 20 normal controls, but very few subjects with low platelet counts.

Patients and methods

Three hundred in- and outpatients were recruited into the study, most of whom were in the care of the haematologists. This patient group was selected because of its high incidence of thrombocytosis. The local ethics committee (Bromley LREC) granted approval for the study. All the patients were over 18 years old and written consent was obtained.

For each patient blood was collected into three blood tubes containing serum separator gel, lithium heparin or potassium EDTA (greiner bio-one). The lithium heparin and gel tubes were centrifuged within 2 h and the plasma and serum potassium was measured within 4 h. Samples were centrifuged for 5 min at 3000 rpm using a Heraeus Labofuge 400. Potassium measurements were carried out using Bayer ADVIA 1650 indirect ISE methodology. The blood platelet counts were performed on Bayer ADVIA 120 analysers.

Any samples which showed haemolysis on visual inspection were rejected. Similarly, any sample sets where the white cell count was above $20 \times 10^9/\text{L}$ were rejected. This left a total of 266 sample set results available for statistical analysis. The difference between serum and plasma potassium (serum–plasma) was plotted against the platelet count for each sample set. Platelet counts for this patient group were evenly spread, with 80 subjects having counts above the reference range ($150\text{--}450 \times 10^9/\text{L}$) and 51 subjects having low counts, the remainder (135) being within the reference range.

Practical aspects of checking haematology results

Using an ACT Apex pathology computer system, it has been a simple four key-stroke process to view the haematology data directly from the biochemistry results authorization screen. In practice, haematology results have normally been available before biochemistry measurements. Haematology and Biochemistry staff have been able to view data for both departments prior to technical validation.

Results

Regression analysis (SPSS 10) demonstrated a linear relationship between platelet count and serum–plasma potassium. There was a statistically significant correlation: $r^2 = 0.41$ ($P < 0.0001$). The equation of the regression line was:

$$\text{Predicted serum–plasma potassium} = -0.058 + (0.00113 \times \text{Platelet count})/10^9 \text{ (see Figure 1).}$$

Although there were only eight samples with platelet count $>1000 \times 10^9/\text{L}$, excluding these points had very little effect on the regression line. All results have therefore been included.

From the equation it may be seen that serum potassium elevations relative to plasma values of 0.3, 0.4 and 0.5 mmol/L could be expected at platelet counts of 317×10^9 , 400×10^9 and $494 \times 10^9/\text{L}$, respectively. However, it is not suggested that the correlation is good enough to apply corrections to serum potassium measurements based on platelet count.

The sensitivity and specificity of platelet thresholds were calculated for various potassium differences. In this study, an elevation of more than 0.5 mmol/L was taken to be significant for statistical calculations.

Figure 2 shows a plot of sensitivity and specificity for the various platelet thresholds.

Discussion

Selecting optimum sensitivity and specificity

Serum potassium was affected by platelet count and the magnitude of the elevation was proportional to platelet count. Even platelet counts at the upper limit of the normal range appear to be associated with some elevation in serum relative to plasma potassium. Compared with our established platelet threshold of $500 \times 10^9/\text{L}$, lower thresholds gave greater sensitivity for elevations of >0.5 mmol/L, but with loss of specificity. A lower threshold would therefore result in more frequent inappropriate withholding of results.

Even with quite high platelet counts, it is not inevitable that an artefactual elevation in serum potassium

Figure 1 Linear regression of platelet count plotted against observed serum–plasma potassium difference.

Figure 2 Sensitivity and specificity of various platelet counts for a (serum-plasma) potassium difference threshold of >0.5 mmol/L.

will be observed. Using our current threshold ($500 \times 10^9/L$), a positive predictive value of 67% is achieved. Therefore, two out of three withheld results will indeed be cases of pseudohyperkalaemia, but one will be inappropriately withheld.

Considerable inter-individual variation has previously been documented⁷ showing that haematocrit is also relevant to the magnitude of potassium elevations. These workers noted that patients with thrombocytosis and polycythaemia vera showed a more rapid release of potassium than others. They calculated that the increment in potassium would be three-fold higher for a patient with a haematocrit of 0.7 than a patient with haematocrit of 0.1, due to the smaller extracellular volume of distribution available. They noted that in polycythaemia haematocrit is high and concluded that this would explain the greater tendency to pseudohyperkalaemia.

In another study, Lutomski *et al.*⁶ predicted elevations in serum potassium of 0.56 and 0.96 mmol/L at platelet counts of $500 \times 10^9/L$ and $1000 \times 10^9/L$, respectively. That compares well with this study, in which equivalent figures are 0.51 and 1.07 mmol/L. However, Lutomski obtained a higher correlation coefficient and suggested that it could be practical to adjust potassium results for platelet count if plasma were not available. Another study⁵ has retrospectively examined platelet counts and serum potassium values rather than comparing paired plasma and serum values, predicting increases in serum potassium of 0.7 mmol/L at platelet counts of $1000 \times 10^9/L$.

Selecting the potassium threshold for checking platelet count

Ideally all samples for which serum potassium is determined should have platelet count checks. It is impor-

tant to note that severe hypokalaemia may be masked. Among haematology patients, few have both hypokalaemia and thrombocytosis. Of our 266 patients, only one had both hypokalaemia and platelets above $500 \times 10^9/L$, and the serum and plasma potassium results were similar.

The effect of applying a platelet check for serum potassium results >5.4 mmol/L was investigated by scrutinizing 2959 consecutive serum potassium results obtained between 30 June and 7 July 2004.

Of the total potassium measurements, 68 results were >5.4 mmol/L. These results were for 52 patients as some had had more than one measurement. Of the 52 patients, full blood counts were available for 37 and six of these had platelet counts above $500 \times 10^9/L$ (approximately 16%). All six were in-patients, but requests for plasma samples produced repeat samples for only two patients. Hyperkalaemia was confirmed for one patient, but was spurious for the other.

Plasma values and paradoxical results

Serum potassium values were not invariably higher than plasma values. There was a tendency for samples with very low platelet counts to have higher plasma values than serum values. No explanation has been found for this.

Plasma has been recommended as the ideal matrix for potassium determination.⁸ However, a major problem is that this medium is unsuitable for many other laboratory tests. The presence of small fibrin clots in plasma samples is also a disincentive as these can cause blockages within the high-throughput autoanalysers, leading to considerable delays. Therefore, many laboratories continue to use serum for electrolyte analysis.

Sometimes, unexpected or unlikely hyperkalaemia may be observed for patients for whom no haematology has been requested. These results would not be withheld in the absence of evidence of haemolysis, contamination or delayed sample receipt. A comment inviting the clinician to repeat the test on both serum and plasma, together with a full blood count, would be added at the discretion of the person responsible for clinical validation of the results.

Conclusion

A platelet count threshold has been validated for withholding high serum potassium results.

If a serum potassium result reaches telephoning limits, it is desirable to check the haematology data when a paired sample is available. If the platelet count is $>500 \times 10^9/L$, a lithium heparin sample should be requested as a matter of urgency.

Additionally, a warning comment can be attached to any haematology results with platelet counts above this threshold to alert clinicians to the possibility of spurious serum potassium results. These simple measures are very easy to implement, particularly where clinical chemistry and haematology departments are unified.

The incidence of hyperkalaemia among all patients during a seven-day study period in July 2004 was 2.3%. The incidence of thrombocytosis among those patients with hyperkalaemia (potassium > 5.4 mmol/L) during the period selected was 16%, so that six potentially spurious results were withheld during the seven-day period. Over a 12-month period, it is anticipated therefore that around 300 potentially spurious results are avoided.

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