DANGER OF RELIANCE ON BLOOD UREA ESTIMATION

R. Ashcroft, B.A. Clarkson, R.W. Elliott, D.B. Horn, D.N.S. Kerr, A.M. Robson*

When the Artificial Kidney Unit was opened at Newcastle in 1959, dialysis was usually carried out at a specified blood urea level (350-400 mg.%). The belief that it was unnecessary to refer patients until their blood urea approached this level spread in spite of protest, and dies hard. The hazards of this form of brinkmanship are further increased if blood urea estimations are unreliable in the referring hospital. Over the last 5 years more than 20 patients have been admitted at a dangerously late stage of renal failure because of reliance on wildly inaccurate blood urea estimations (more than 20% discrepancy between two laboratories). A wide variation between blood urea results from different laboratories has also been reported in several previous investigations of laboratory accuracy.

CAUSES OF ERROR IN BLOOD UREA ESTIMATION

In this series, false low results were more common than false high results. Most of the erroneous estimations were carried out by experienced technicians but many were done on 'emergency service'. Almost all were carried out manually, using urease and Nessler's reagent. Further details were difficult to obtain in retrospect and the following investigations were therefore carried out in our own laboratories.

1. Comparison between manual (urease/Nessler) and Autoanalyser (Diacetyl Monoxime) methods.
   
   Zilva and London (1962) reported a systematic difference between these methods at high blood urea levels in some patients, which might have explained a few of our discrepancies. Our simultaneous estimations by the two methods are shown in Figures 2a and 2b. There is a close agreement up to a level of 200 mg.% and a wider scatter thereafter. Although no systematic difference is obvious from the graph, an enlarged series at higher levels (above 200 mg.%) showed that the manual method gave a slightly lower result. In 52 comparisons on 11 patients the urea results were 98.3% those by Autoanalyser (0.05 > p > 0.02). In one patient with a plasma urea of 600 mg.% the discrepancy between the methods was 10% and this was confirmed by 9 autoanalyser and 38 manual estimations on the same sample (p<0.01).
   
   This slight methodological difference is not clinically important.

2. Reliability of both methods.
   
   Agreement between duplicates in the same batch was good. Mean difference between duplicates (200 specimens):
   
   Manual 1.4%
   Autoanalyser 1.0%

   However day-to-day reliability, tested on same specimen, was less satisfactory:

*From the Departments of Medicine and Clinical Biochemistry, The Royal Victoria Infirmary and General Hospital, Newcastle upon Tyne.
Recovery experiment - correct result 422 mg.%

<table>
<thead>
<tr>
<th></th>
<th>Error of mean (10 estimates)</th>
<th>Mean error of daily estimates</th>
<th>Error Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual</td>
<td>0.8%</td>
<td>4.5%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Autoanalyser</td>
<td>2.0%</td>
<td>2.7%</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

This and similar experiments show that most of the scatter in Figure 2b is due to variation in the manual method. Although disturbing, this does not explain the gross errors encountered in clinical practice. We presume these are due to some deviation from correct procedure and have checked the method for likely sources of error at high urea levels.

   (a) Urease
   The urease from one supplier proved defective as it gave a high blank reading which might pass unnoticed. All batches of urease Dunning tested were satisfactory and the recommended quantity was adequate for undiluted plasma from all patients encountered (plasma urea up to 600 mg.%).

   (b) Temperature and time of incubation
   No change in accuracy was found with temperatures between 37 and 45°C and with incubation times between 15 and 60 minutes.

   (c) Predilution of plasma
   Predilution did not affect accuracy provided protein precipitation agents were also diluted.

   (d) Dilution before adding Nessler's
   If a high result is unexpected Nessler's reagent is added to the wrong dilution of supernatant. We suspect that this is a common source of gross error, particular in 'emergency ureas'. A fine precipitate may form which is not visible to the naked eye but affects the light absorption. Depth of colour may no longer bear a linear relationship to concentration.
   Example: Correct result 407 mg.%
   Supernatant undiluted: 300 mg.%.

4. Possible sources of error applicable to all methods.
   Blackmore and Elder (1961) suggested that urea might be concentrated in cells in some uraemic subjects. If this were so anomalous results might be obtained by using whole blood, by delay in separation of plasma or by ischaemic exercise of the forearm before venipuncture.

Comparison of whole blood and plasma (separated without delay in 12 uraemic patients).

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean whole blood</td>
<td>266 mg.%</td>
</tr>
<tr>
<td>Mean plasma</td>
<td>267 mg.%</td>
</tr>
</tbody>
</table>

Comparison of arterial plasma with venous plasma after 2 minutes ischaemic exercise in 6 uraemic patients.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>274</td>
</tr>
<tr>
<td>Venous</td>
<td>275</td>
</tr>
</tbody>
</table>

We conclude that no important error is introduced by tourniquet, delayed separation or haemolysis.
UREA AS AN INDEX OF CLINICAL URAEMIA

Although urea is the most popular index of azotaemia it correlates rather poorly with some symptoms. Figure 3 shows the plasma urea and urate (both by Autoanalyser) in a series of uraemic patients with and without pericarditis. The patients with pericarditis are separated better by plasma urate than by plasma urea.

Plasma urea becomes even less reliable as a measure of clinical state after repeated haemodialysis which removes urea preferentially. Figure 4 illustrates the onset of severe mental disturbance and EEG change in spite of an improving plasma urea level. An increase in dialysis time from about 10 to 20 hours per week was followed by remission of symptoms without any striking change in average blood urea level.

CONCLUSION

In view of the pitfalls in the estimation and interpretation of high blood urea levels it is probably safer to use 2 or 3 indices of azotaemia simultaneously, and act on the most abnormal result.

REFERENCES


Figure 1.