Concurrent estimation of total body and exchangeable body sodium in hypertension

Scottish Universities Research and Reactor Centre, East Kilbride, Glasgow, and the (1)MRC Blood Pressure Unit and (2)University Department of Medicine, Western Infirmary, Glasgow, Scotland, U.K.

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Summary

1. Total-body neutron-activation analysis in vivo was carried out in 11 hypertensive subjects to measure simultaneously the total body content of sodium, chlorine, calcium, phosphorus and nitrogen.

2. There was a highly significant correlation between total body sodium measured by activation analysis and total exchangeable sodium measured by a standard isotope-dilution technique ($r = 0.92, \ P < 0.001$). Exchangeable sodium averaged 80-3% of total body sodium.

3. The measured values of chlorine, calcium, phosphorus and nitrogen were similar to those for healthy subjects reported by others.

4. Activation analysis in vivo appears promising as an additional tool for investigating sodium metabolism in hypertension, as it is the only method available for determining the total body content of this element. The radiation dose (1 rem) is sufficiently low to permit repeated measurements in the same subject.

Key words: calcium, chlorine, hypertension, nitrogen, phosphorus, sodium, total-body neutron-activation analysis in vivo.

Abbreviations: TB, total body (sodium, calcium, chlorine, nitrogen etc.); Na_e, total exchangeable sodium.

Introduction

The discrepancy between total body sodium (TBNa), determined chemically post mortem (Wildowson, McCance & Spray, 1951; Forbes & Lewis, 1956) and total exchangeable sodium (Na_e) measured by isotope dilution (Edelman, James, Boden & Moore, 1954; Miller & Wilson, 1953) indicates the presence of a non-exchangeable (or slowly exchangeable) sodium pool, probably in bone (Edelman et al., 1945; Norman, 1963; Comar, Riviere, Raynaud & Kellershohn, 1968). Clinical studies of sodium metabolism use Na_e as an index of TBNa, which assumes that the ratio Na_e/TBNa is constant. However, earlier reports, in which TBNa was assessed by activation analysis in vivo with simultaneous measurement of Na_e, are conflicting (Anderson, Battye, Osborn, Tomlinson, Fry & Newton, 1972; Chamberlain, Fremlin, Peters & Philip, 1968; Rudd, Palithorp & Nelp, 1972). Furthermore, in some conditions non-exchangeable bone sodium may possibly change (Streeten, Rapoport & Conn, 1963; Hosking, Chamberlain, Fremlin & James, 1972).

Sodium metabolism can be deranged in hypertension but we know of no comparisons of Na_e and TBNa in hypertensive subjects. We have therefore carried out a pilot study in 11 patients to assess how useful such concurrent estimations might prove. In view of the exploratory nature of this investigation, a homogeneous group of patients was not selected.
Method

Patients (Table 1)

Eleven hypertensive patients were studied: four with essential hypertension, five with primary hyperaldosteronism, one with renal artery stenosis and one with polycystic kidneys. In two patients with primary hyperaldosteronism in whom surgery had not been performed, the presence or absence of an adrenocortical adenoma was predicted by the statistical technique of quadric analysis (Aitchison, Brown, Ferriss, Fraser, Kay, Lever, Neville, Symington & Robertson, 1971).

Body sodium estimations

Total body sodium, chlorine, calcium, phosphorus and nitrogen were measured simultaneously by activation analysis using 14 MeV neutrons as described previously (Boddy, Holloway & Elliott, 1973). The patient, lying on a motorized couch, passed between two sealed tube neutron generators (Philips type no. 18602), and received a dose of 1 rem by simultaneous bilateral irradiation. Induced radioactivity was then measured in a high-sensitivity shadow shield whole-body counter (Boddy, Elliott, Robertson, Mahaffy & Holloway, 1975) in which the patient passed between two large sodium iodide detectors (29.2 cm diameter and 10.2 cm deep). Correction for radioactive decay associated with the scanning procedure was achieved automatically for all induced radioisotopes by using an identical scanning speed for both irradiation and radioactivity counting. Repeated counting scans were performed up to 40 min after irradiation to obtain measurements of the radionuclides which have different half-lives. Calibration factors for the elements activated were obtained with three water-filled polyethylene phantoms with respective body weights of 52, 73 and 83 kg and heights of 153, 173 and 178 cm. Known amounts of the elements were put into the phantoms, which also had predetermined amounts of calcium and phosphorus in 'pseudo-bone' distributed anthropomorphically. An extensive calibration programme, to be reported elsewhere, showed that the calibration was influenced little by body habitus; nevertheless patients were matched by body weight to the corresponding phantoms.

Exchangeable body sodium ($\text{Na}_e$) was measured at 24 h (Davies & Robertson, 1973), from $^{24}\text{Na}$ given the day after the TBNa estimations. Values are given as mean ± SEM. Comparisons were made by paired $t$-test and Wilcoxon's signed ranks test. The procedures were approved by the MRC Panel on in vivo Activation Analysis, the Technical Panel of the Scottish Advisory Committee on Radioisotope Services and the Western Infirmary Ethical Supervisory Committee. All patients gave informed consent.

Results

There was a highly significant correlation ($r = 0.92, P < 0.001$) between TBNa and $\text{Na}_e$ (Table 1). The regression equation was $\text{TBNa} = 924 + 0.895 \text{Na}_e$, the standard deviation from regression on the mean TBNa being 234 mmol (7.0%). Mean TBNa ($3324 ± 169$ mmol) was significantly greater ($P < 0.001$) than mean $\text{Na}_e$ ($2440 ± 173$ mmol).

Non-exchangeable sodium was calculated as the difference between TBNa and $\text{Na}_e$ and expressed as a percentage of TBNa: the mean value was 19.60 ± 2.15%. In all untreated patients the mean value was 16.66 ± 3.46% and in patients taking spironolactone or amiloride 23.32 ± 1.20%. These mean percentages were not significantly different ($P > 0.1$). When the non-exchangeable sodium was related to body weight and to total body nitrogen, similar findings were obtained.

The measured values of TBNa and $\text{Na}_e$ are compared in Table 1 with the expected 'normal' values derived from height and weight by using the relationships of Ellis, Vaswani, Zanzi & Cohn (1976) and of Skrabal, Arnot & Joplin (1973) respectively. In all of the untreated patients either TBNa or $\text{Na}_e$, and in some cases both, were greater than the expected normal amounts. Only one value was greater than that expected in the treated patients.

The measurements obtained for total body calcium (TBCa), chlorine (TBC1), phosphorus (TBP) and nitrogen (TBN) are summarized in Table 1 and are in keeping with reference values for a typical normal subject (I.C.R.P. Publication, 1975).

Discussion

The limited aims of this pilot study were to demonstrate the clinical acceptability of our technique and the potential usefulness of activation analysis in vivo in hypertension of various aetiology and also to compare TBNa with both
TABLE 1. **Summary of findings for 11 hypertensive subjects**

Values in parentheses are pretreatment measurements. E.H. = essential hypertension; R.A.S. = renal artery stenosis; P.H. = primary hyperaldosteronism; Q.A. = adenomatous on quadric analysis; Q.N. = non-adenomatous on quadric analysis; P.K. = polycystic kidneys; A = amiloride 40 mg/day; S = spironolactone 400 mg/day; Naₑ = exchangeable sodium; TBNa = total body sodium; TBCa = total body Ca; TBCl = total body chlorine; TBP = total body phosphorus; TBN = total body nitrogen. Plasma renin values are in international units (Bangham, Robertson, Robertson, Robinson & Tree, 1975).

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Blood pressure (mmHg) at time of study (pretreatment)</th>
<th>Plasma values</th>
<th>Total body values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>54</td>
<td>155</td>
<td>72.0</td>
<td>E.H.</td>
<td>Nil</td>
<td>204/110 (260/125)</td>
<td>Renin 47 (µ.u./ml)</td>
<td>Naₑ 2624</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>42</td>
<td>186</td>
<td>89.4</td>
<td>E.H.</td>
<td>Nil</td>
<td>142/100 (220/122)</td>
<td>Angiotensin II 373 (28)</td>
<td>TBNa 1979</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>46</td>
<td>148</td>
<td>164</td>
<td>R.A.S.</td>
<td>P.H. (Q.A.)</td>
<td>180/104 (220/122)</td>
<td>Aldosterone 370 (5)</td>
<td>TBCa 2672</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>55</td>
<td>173</td>
<td>175</td>
<td>P.H.  (Q.A.)</td>
<td>Nil</td>
<td>165/115 (195/105)</td>
<td>Potassium 230 (10)</td>
<td>TBCl 4685</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>40</td>
<td>175</td>
<td>177</td>
<td>P.H.</td>
<td>Nil</td>
<td>172/90 (220/122)</td>
<td>Sodium 68 (24)</td>
<td>TBC (g) 685</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>47</td>
<td>164</td>
<td>178</td>
<td>E.H.</td>
<td>S</td>
<td>160/100 (195/105)</td>
<td>Aldosterone 6 (13)</td>
<td>TBCI 1664</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>42</td>
<td>178</td>
<td>163</td>
<td>E.H.</td>
<td>S</td>
<td>146/80 (168/100)</td>
<td>Potassium 46 (7)</td>
<td>TBN (g) 1173</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>55</td>
<td>177</td>
<td>163</td>
<td>E.H.</td>
<td>S</td>
<td>170/100 (180/118)</td>
<td>Sodium 46 (7)</td>
<td>TBN (g) 1173</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>59</td>
<td>164</td>
<td>167</td>
<td>P.H.</td>
<td>S</td>
<td>116/78 (180/118)</td>
<td>Aldosterone 113 (5)</td>
<td>TBN (g) 1173</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>70</td>
<td>163</td>
<td>163</td>
<td>E.H.</td>
<td>S</td>
<td>175/85 (180/118)</td>
<td>Potassium 46 (7)</td>
<td>TBN (g) 1173</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>40</td>
<td>167</td>
<td>167</td>
<td>P.K.</td>
<td>A</td>
<td>160/110 (180/118)</td>
<td>Sodium 46 (7)</td>
<td>TBN (g) 1173</td>
</tr>
</tbody>
</table>

* Typical adenoma subsequently removed surgically.
concurrent estimates of $N_a$, and values quoted in the literature.

All patients found activation analysis acceptable. The procedure involved no discomfort, the patient simply lying on a motor-driven couch both for irradiation and radioactivity counting. The whole-body radiation dose is 1 rem, which may be compared with X-ray doses to the bone marrow or gonads of at least this value during such procedures as urography and fluoroscopy and with the dose of 5 rem permitted annually for occupationally exposed persons (I.C.R.P. Publication, 1966).

Repeated measurements on anthropomorphic phantoms have shown that the reproducibility is 2-3% (Boddy et al., 1973) and our sequential studies in patients with other disorders confirm this estimate of precision (unpublished work). Repeated measurements by activation analysis over a period of years should therefore provide accurate data with the minimum of inconvenience to the patient, as only outpatient visits are required, without urinary or faecal collections.

The International Commission on Radiological Protection Task Group has made an extensive and critical survey of the literature relating to body composition and has derived anatomical, elemental and physiological values to typify a 70 kg ‘Reference Man’ (I.C.R.P. Publication, 1975). Values were obtained analogously for woman. In our subjects, the findings for TBCa, TBCi, TBP and TBN are similar to the reference values. However, as others have also observed, values for TBNa are less than the reference values (I.C.R.P. Publication, 1975), which may therefore have been overestimated. TBNa and $N_a$ were highly correlated in our patients and, generally, were similar to the expected normal values, although there was suggestive evidence of some interesting deviations. $N_a$ represented 80-3% of TBNa, which compares with earlier values of 82-3% (Chamberlain et al., 1968), 72-7% (Rudd et al., 1972) and 91-6% (Anderson et al., 1972). The technique of measuring concurrently TBNa and $N_a$ allows estimation of non-exchangeable sodium, which may vary in patients with primary hyperaldosteronism (Streiten et al., 1963). In this context, the three untreated patients with essential hypertension and the patient with untreated hyperaldosteronism had the lowest values of non-exchangeable sodium: 11-2% 6-5%, 15-1% and 14-3% (mean 11-8%), whereas the values in the treated patients or those having renal involvement ranged from 19-8 to 30% (mean 24-2%). Although these results require confirmation, we have been encouraged sufficiently by our initial experience to use this procedure sequentially to assess various types of treatment in patients with raised arterial blood pressure of different aetiology.

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