Differences in Serum Potassium Concentrations in Normal Men in Different Geographic Locations

Marcus M. Reidenberg, 1 Zhi-Ping Gu, 2 Beverly Lorenzo, 1 Elsimar Coutinho, 3 Celia Athayde, 3 Julian Frick, 4 Frank Alvarez, 5 Vivian Brache, 5 and E. Ejio Emeuayan 6

Hypokalemia has been associated with the taking of gossypol, a potential oral antifertility drug for men. Because the frequency of this response differed in different parts of the world, this study was done to learn if "normal" serum [K+] also differed. [K+] was measured by flame photometry in serum from apparently normal men from Austria (n = 30), China (53), Brazil (100), the Dominican Republic (38), and the US (103), and in plasma from Nigerian men (82). The mean (SD) for [K+] in Chinese men, 3.82 (0.27) mmol/L, was lower than that in Brazilians [4.06 (0.29) mmol/L], Austrians [4.14 (0.44) mmol/L], Dominicans [4.37 (0.33) mmol/L], or Americans [4.38 (0.37) mmol/L]. Apparently there are regional differences in average serum [K +] with men in China having lower serum [K+] than men elsewhere. This may predispose them to hypokalemia.

Additional Keyphrases: hypokalemia · flame photometry · variation, source of · reference values · gossypol · contraceptives

Gossypol, a substance in cotton seed, has an antifertility effect in men and is under development as an oral contraceptive for men. The drug inhibits spermatozoa motility and then decreases the sperm count without affecting the hormonal function of the testes (1). It is the only compound known to have this effect in man.

In clinical trials in China, some of the men taking gossypol developed hypokalemia (1), which markedly slowed the development of this agent as an oral contraceptive for men. Hypokalemia had not been seen in small trials of gossypol elsewhere (2), and a decrease in serum potassium was observed in controls as well as in gossypol-treated subjects in a trial in Beijing (3). Whereas hypokalemia was seen in men taking gossypol in Nanjing, it also occurred, but with a lower frequency, in men not taking gossypol (4). Because the frequency of hypokalemia in men taking gossypol differed in different parts of the world (1), we performed the present study to learn whether "normal" serum potassium concentrations in men differed in different parts of the world. This study was approved by the Cornell University Medical College Institutional Review Board.

Subjects and Methods

Blood from apparently normal healthy male volunteers, ages 18—55 years, was collected and allowed to clot, and the serum was removed and frozen in all sites but Nigeria; in Nigeria, heparinized blood was collected and the plasma was removed and frozen. All samples were shipped frozen to Cornell University Medical College (except for 20 samples from Brazil and all of the samples from Nigeria, which thawed en route), where the potassium concentration was measured with an Instrumentation Laboratory (Lexington, MA) Model 943 flame photometer. The instrument was calibrated with Instrumentation Laboratory’s Na+/K+ 140/5 mmol/L plasma or serum standard. This single-point calibration was checked with our own standards, which were made to contain K+ at 3.25 and 4.25 mmol/L and assayed in duplicate with the calibration standard. The samples were analyzed in duplicate in trays containing 32 specimen wells. Each tray was calibrated with the instrument’s standard, checked with our standards, and the calibration was automatically checked after the 16th analysis and the last analysis of each tray. Samples whose duplicates differed by more than 0.07 mmol/L were reanalyzed. In a blinded assessment of analytical quality involving split samples from 10 subjects, the intra- and interday CVs were both 0.8%.

Blood was collected from 30 staff members of the Department of Urology of the general hospital in Salzburg, Austria; from 53 managing workers in a large factory in Shanghai, China; and from 100 men coming to a family planning clinic for vasectomies in Salvador, Bahia, Brazil, during December 1988—January 1989; from 52 men in Newark, NJ, and 51 men in Philadelphia, PA, who were being screened to join the normal volunteer pools of two pharmaceutical manufacturers’ clinical pharmacology facilities during the summer and fall of 1990; from 38 men attending a family planning clinic in Santo Domingo, Dominican Republic, during December 1990—February 1991; and from 82 men in Lagos, Nigeria, during the summer of 1991. The samples from Austria were drawn 2—4 h after the subjects had eaten a light continental breakfast. All other subjects had their blood drawn in the morning while fasting.

Results and Discussion

The frequency distributions of the serum potassium concentration values for some of the populations are
Table 1. Average Blood Potassium Concentration Values in Men Living in Different Cities

<table>
<thead>
<tr>
<th></th>
<th>No. of subjects</th>
<th>K⁺, mmol/L</th>
<th>Mean</th>
<th>SD</th>
<th>No. (%) &lt;3.5 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shanghai, China</td>
<td>53</td>
<td>3.82</td>
<td>0.27</td>
<td>5(9)</td>
<td></td>
</tr>
<tr>
<td>Salvador, Brazil</td>
<td>100</td>
<td>4.06</td>
<td>0.29</td>
<td>3(3)</td>
<td></td>
</tr>
<tr>
<td>Salzburg, Austria</td>
<td>30</td>
<td>4.14</td>
<td>0.44</td>
<td>1(3)</td>
<td></td>
</tr>
<tr>
<td>Philadelphia, PA</td>
<td>51</td>
<td>4.31</td>
<td>0.32</td>
<td>0(0)</td>
<td></td>
</tr>
<tr>
<td>Newark, NJ</td>
<td>52</td>
<td>4.45</td>
<td>0.41</td>
<td>1(2)</td>
<td></td>
</tr>
<tr>
<td>Santo Domingo, Dominican Republic</td>
<td>36</td>
<td>4.37</td>
<td>0.33</td>
<td>0(0)</td>
<td></td>
</tr>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibadan, Nigeria</td>
<td>82</td>
<td>3.85</td>
<td>0.67</td>
<td>17(21)</td>
<td></td>
</tr>
</tbody>
</table>

* The value for the Nigerians averages less than for serum samples because the potassium in platelets is not released into plasma but is released into serum.

results, which were from serum samples. Analysis of variance of the serum results gave an F value of 25.69 (P <0.001). The Chinese values are statistically significantly lower (P <0.05 with the Bonferroni correction) than all the rest; the Brazilian mean is lower than that for the group from Santo Domingo and the two US groups, and the Austrian values are lower than those for the men from Newark but not for those from Philadelphia or Santo Domingo. The Newark and Philadelphia results are not different from each other and have a combined mean (SD) of 4.38 (0.37) mmol/L, which is not different from the Santo Domingo results.

This observation of different frequency distributions of serum potassium concentration values in men from different parts of the world raises several questions. Given that the average values for men in Shanghai are lower than those in the other locations in our study and that the values from Brazil are lower than those from the US, does this mean that the range of "normal" values should also be lower for these places?

Current "normal" potassium values were established by measuring serum or plasma potassium concentra-
tions in groups of normal subjects, usually from the US, in the 1940s and 1950s after the flame photometer was commercialized. Reported normal mean values in mmol/L (SD, n), were 4.52 (0.45, 107) (5), 4.06 (0.26, 103) (6), and 4.41 (0.36, 70) (7). Glenn and Shannon (8) measured serum potassium in 20 normal men four times per week for 4 weeks; the mean potassium concentrations ranged from 4.14 to 5.00 mmol/L on the different days, with the mean (SD) of the daily means being 4.45 (0.29). Our values from Newark and Philadelphia are the same as these literature values. Values reported from India were even higher, being 4.90 (0.29) mmol/L (n = 24) (9).

Regional differences in dietary potassium intake may explain part of the regional differences in serum potassium values. The 24-h urinary excretion of potassium has been used as a measure of intake, and the following mean or median values have been reported (in mmol/24 h): in China—Beijing 34 (10) and 44 (11), Nanjing 26 (10), Tianjin 33 (10), and Shanghai 28 (11); in Brazil—Xingu 81 (10), Yanomamo 58 (10), and Porto Alegre 51 (11); in the US—Evans County, GA, white men 40 (12) and black men 24 (12), Chicago 53 (10), Jackson, MS, black 38 (10), Jackson, MS, white 54 (10). Most of the Chinese values are lower than the others, which may explain part of the difference in serum potassium concentrations, although it does not explain why Brazilian values are lower than US values. A recent extensive nutritional survey in China (13) found a mean plasma potassium of 4.51 mmol/L and extrapolated a urinary potassium value of 67 mmol/24 h for all of China. The respective mean values for Shanghai men were 4.74 mmol/L and 49 mmol/24 h (13). The observation of both lower urinary values and higher plasma potassium values in Shanghai men than the Chinese averages makes it difficult to integrate data from that study with ours.

Another difference between Chinese men and American white men that may contribute to the different potassium values is a difference in their β-adrenergic systems. Catecholamines stimulate the β-2 receptors, causing a decrease in serum potassium (14), probably by stimulating its uptake into skeletal muscle (15, 16). Zhou et al. showed that Chinese men are much more sensitive to propranolol than are American white men (17) and that this increased sensitivity is not due to differences in the pharmacokinetic behavior of propranolol between the two groups (18, 19) or in β-receptor density or affinity of their lymphocytes (17).

The common occurrence of hypokalemic periodic paralysis in thyrotoxic Chinese men, in comparison with European or North American men, may be related to the serum potassium concentrations being lower in some normal Chinese populations than in all the other populations we studied. The incidence of periodic paralysis in thyrotoxic Chinese men is 13% (20). In China, attacks of paralysis in thyrotoxic patients occur mainly in the summer months and are precipitated by high carbohydrate intake (20, 21). Propranolol pretreatment decreases the frequency of attacks and diminishes their intensity when they do occur (21).

The effect of climatic variation on plasma potassium concentration has been studied. In southern India, plasma potassium values were lower during the monsoon season in November than at other times of the year (22). A study in Germany of 78 healthy male and female subjects found no difference in serum potassium concentrations between sera taken in summer from those taken in winter. A subset of 32 subjects studied over an 18–30 °C temperature range also showed no differences in serum [K+] (23). Thus, ambient temperature, as such, apparently has little effect on serum potassium. Other factors must play a role in the seasonal peak of instances of thyrotoxic periodic paralysis in China in summer and the nadir in winter.

Many attempts to produce hypokalemia in various animal species by giving them gossypol have failed (24). Recently, Lohiya et al. (25) found that adult male langur monkeys given gossypol (5 mg/day for 120 days) had a decrease in serum potassium, an increase in urine potassium, and a decrease in urine sodium. Perhaps the low average serum potassium in some normal Chinese men in China predisposes them to develop hypokalemia, a predisposition that may not be present in the usual laboratory animals.

Another possible implication of our observation of low serum potassium in the Shanghai population concerns the sudden deaths among refugees and construction workers from Southeast Asia. The mechanism for this sudden death is unknown at this time (26). Thiamine deficiency (27, 28) and hypokalemia (29) have been postulated as being involved. Our observation of low average serum potassium values in Chinese, if extended to other Asian populations, could indicate that these people are at risk for the development of clinically significant hypokalemia.

The fact that some Chinese populations have serum potassium values within the usually accepted range of normal (13, 30) suggests that the low values we observed in the population of Shanghai men in our study was due to environmental rather than genetic factors.

We thank Leslie Hanson de Moura, Susana K. Denis, Anthony Piraino, and You Gen-di for their help with this research. Supported in part by a grant from the Rockefeller Foundation to Cornell University and by grants from the Rockefeller Foundation in support of South-to-South Collaboration in the Population Sciences and Reproductive Health.

References