Upsala J Med Sci 98: 387–393, 1993

6.2.1 The Basis for Common Reference Intervals for Serum Potassium

Mogens Stig Djurhuus,[1] Per Hyltoft Petersen,[1] Allan Rohold,[2]
Sten Vadstrup[2] and Adam Uldall[3]

[1]*Department of Clinical Chemistry and* [2]*Medical Department M, Odense University Hospital, 5000 Odense C, and* [3]*Department of Clinical Chemistry, KAS Herlev, 2730 Herlev, Denmark*

ABSTRACT

In order to investigate the relevance of the currently used lower reference limit for S-Potassium in Danish hospital laboratories, analytical bias in the measurement of S-Potassium was compared with the lower reference limit in each of 52 Danish hospital laboratories. The acceptable bias range was estimated according to Gowans et al (1) on the basis of the result of two different reference sample groups.

The estimated acceptable 0.95 bias range was 0.24 mmol/L, so the observed bias range of 0.23 mmol/L was within this limit. As all preanalytical errors tend to increase the measured S-Potassium, all acceptable bias should be in the direction of decreasing the measured value.

It can be concluded that analytical performance allows for more uniform (even common) reference interval(s) in all Danish and perhaps Nordic hospital laboratories, provided that preanalytical errors can be controlled.

CLINICAL SITUATION

Throughout a limited geographical area as Denmark, reference limits for S-Potassium vary considerably. As especially lower reference limit is used as a decision limit for the need of potassium supplementation, it is of interest to have a correct lower reference limit. Hereby, unnecessary potassium supplementation can be avoided. It can be seen from Fig. 1, that an increase in lower reference limit from an estimated "correct" value of 3.4 mmol/L to a value of 3.6 mmol/L would increase the number of "healthy" persons below lower reference limit from 2.5% to 14.1%, leading to misclassification of additionally 11.6% of a healthy population (adopted from Djurhuus et al (2)). The consequence of potassium deficiency is serious, potentially lethal arrhythmias. It is therefore essential to have a correct lower reference limit, and a common reference interval is to be preferred.

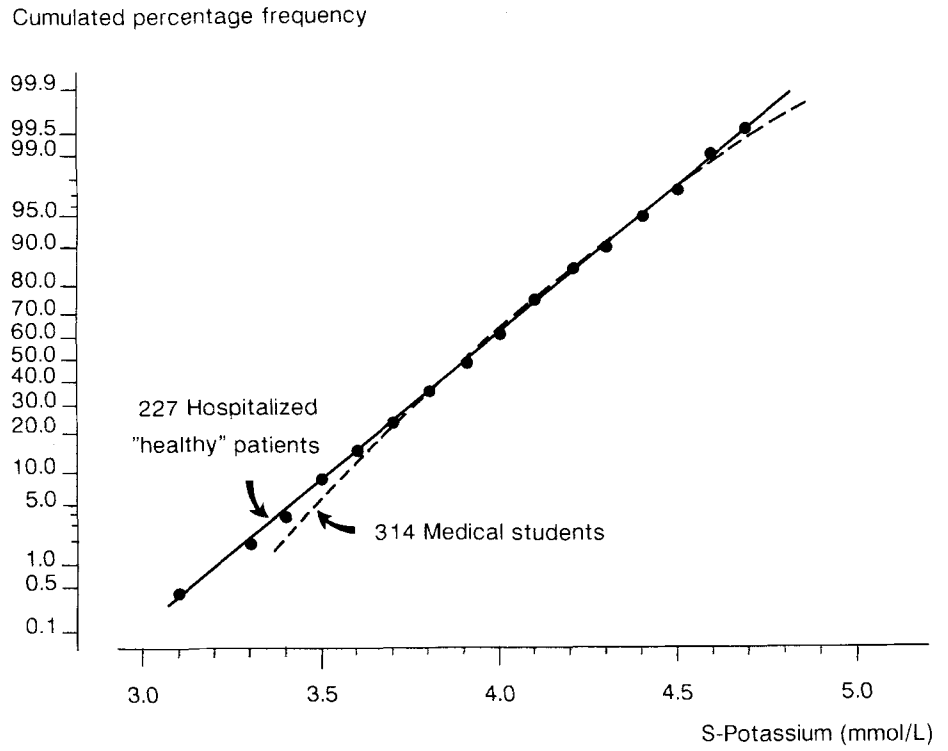

Fig. 1. Probit transformation of the two reference populations. (a) The cumulated percentage frequency values for hospitalized 'healthy' patients (●). The distribution is a Gaussian distribution as indicated by the straight line. The medical students (--) exhibit a more log-Gaussian distribution, but it is still acceptable for statistical treatment with parametric methods. From Djurhuus et al (2) with permission.

CHARACTERISTICS OF THE METHOD

Defining reference interval for S-Potassium.

The material consisted of two different populations

1) 227 patients, who were admitted to Medical Department M, Odense University Hospital during the period 1/1-1979 to 1/9-1987, but who were later discarged without a diagnosis. Median age 52 years, 100 were men.

2) 314 medical students at the 4. year from Odense University Hospital in the period from 1983 to 1987, median age 25 years, 186 were men.

Bias during the relevant period was estimated to +0.05 mmol/L by comparison with standards from NIST (National Institute of Technology and Standards, USA). All values are corrected

accordingly.

The design is fully described elsewere (2).

Currently used reference intervals.

The reference intervals of S-Potassium in the 52 Danish routine laboratories, that participated in the Danish Society for Clinical Chemistry's external quality assesment, 1988 were provided by the individual laboratories.

Estimation of analytical bias in Danish laboratories.

The S-Potassium results from the above mentioned 52 Danish routine laboratories in an external control survey with fresh frozen human sera (3), one specimen containing 3.03 mmol/L was used for estimation of the bias in the relevant concentration for the lower reference limit. Most laboratories determined the potassium-content 5 times (range 2 to 5). For further details refer to Djurhuus et al (2) and Uldall et al (3).

Statistics.

Reference intervals were calculated according to the recommendations from the International Federation of Clinical Chemistry (IFCC) with "Refval" (4), using the parametric estimate. Test for significance were done with Students t-test. Confidence limits (5) were estimated at a 90% or 95% level of confidence as indicated in the corresponding text.

A weak point is, that the time period for the estimation of the reference limits covers several years and it is not the same as the time period for the determination of bias. Another weak point is the lack of determination of preanalytical errors. These include

1) Tourniquet.
2) Haemolysis.
3) Cold storage of blood without separation of serum/plasma.
4) Exercise before or during sampling.
5) Food.

MODEL FOR EVALUATION OF QUALITY SPECIFICATIONS

The determination of reference intervals is an unimodal model. The only paper which addresses the bias in an unimodal model is Gowans et al (1). Tonks (6), Cotlove (7), Barnett (8) and Glick (9) do not specify bias in their models. Harris (10) describes bias according to variance. The two reference samples fulfil the presumptions for use of the model, as the "healthy" hospitalized patients have a clearly Gaussian distribution (Fig. 1) and the medical students have a near-Gaussian distribution (Fig. 1).

The estimated reference values are summarized in Table 1.

Assuming an analytical variation of approximately 0 mmol/L and a reference sample group of 120 persons as proposed by Solberg (4), the goal for using common reference intervals is specified to $|bias| < (0.25 \cdot s_B) \simeq 0.07$ mmol/L, where s_B is the biological (within+between subject) variation and $s_B \simeq 0.30$ mmol/L (Table 1). The 90% confidence interval for the 0.025 fraktile is $\pm 1.65 \cdot SEM = \pm 0.05$ mmol/L. Hereby the goal for the 95% confidence range for measured bias is $2 \cdot (0.07+0.05)$mmol/L=0.24 mmol/L. The observed bias range is 0.23 mmol/L disregarding the two outliers, seen in Fig. 2. This means that the bias range between laboratories is so small, that the requirements for common reference intervals are fulfilled (1).

Table 1. Description of distributions of S-Potassium concentration values for the two reference sample groups, corrected for bias. From Djurhuus et al (2) with permission.

	Hospitalized "healthy" patients		Medical students	
Simple calculations	**Direct values**	**log values**	**Direct values**	**log values**
Mean	3.93 mmol/l	0.60 log conc.	3.94 mmol/l	0.60 log conc.
Standard deviation	0.30 mmol/l	0.30 log conc.	0.28 mmol/l	0.03 log conc.
Skewness	0.007	-0.247	0.397*	0.207
Kurtosis	-0.03	0.339	0.415**	0.556**
Estimated values from "REFVAL"				
Lower reference limit		3.34 mmol/l		3.44 mmol/l
90% confidence interval		3.29-3.40 mmol/l		3.41-3.48 mmol/l
Upper reference limit		4.52 mmol/l		4.53 mmol/l
90% confidence interval		4.47-4.58 mmol/l		4.48-4.59 mmol/l

* $p < 0.01$
** $p < 0.1$

The observed biases from the different laboratories are at both sides of zero. This may be considered a problem, as preanalytical errors all increase the measured value, that is, that the accept interval might better be skew allowing for larger negative bias.

Total preanalytical bias stems from tourniquet, haemolysis, cold storage, exercise (especially with the fist), and food digestion. Haemolysis can be minimized by using plasma (11), and the rest can be controlled rather easily by instructions and training of technicians.

Stress is a special problem. It acutely lowers the S-Potassium, but as the measured value is the actual in vivo level, it cannot be considered as a real part of the preanalytical errors, even though it has profound influence upon the measured value (12). The possibility for more than

one reference interval might therefore be considered.

If all preanalytical errors are controlled, then all the uncertainty can be allowed for analytical bias, as $s_A \simeq 0$ mmol/L. Hereby, the requirements for a common reference interval are fulfilled.

There is minimum influence from matrix effects in the present study, as all potassium determinations are on human sera.

DESIGN OF CONTROL SYSTEM

The present Danish external control system with replicate measurements of a human control serum 5 times a year seems to be sufficient provided the assigned value for potassium is based on a reliable reference method.

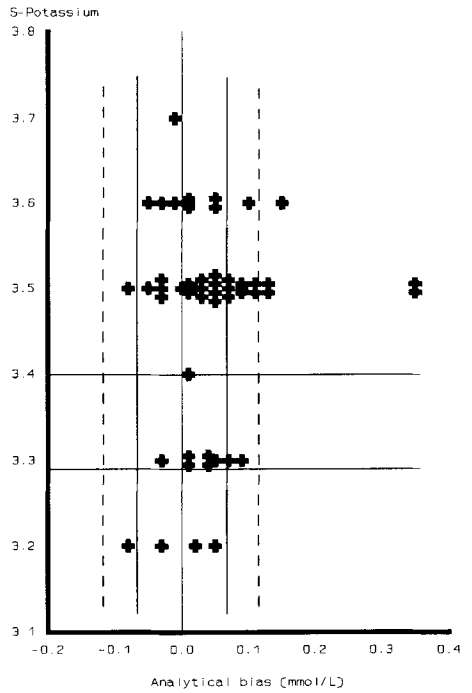

Fig. 2. The relation between lower reference limit and bias in each of 52 Danish hospital laboratories. Indicated is the observed lower reference limit from 227 'healthy' hospitalized persons and acceptable bias. Also indicated (--) is the 95% confidence limits on acceptable bias. Reproduced and slightly changed from Djurhuus et al (2) with permission.

DISCUSSION

The material seems relevant and general, as the patient- and student groups have similar values. The analytical component has a very low coefficient of variation (not measured in this study) of around 2% (13).

The model is valid as it builds on recommendations from the IFCC and general variance interpretations.

CONCLUSIONS

For S-Potassium the biological and analytical basis for establishing a common reference interval in Denmark - and probably all the Nordic countries - is present. If a common reference interval is established, bias in each laboratory should be estimated from 6 to 10 replicates.

The current external control systems in the Nordic countries may be sufficient for the purpose provided a valid target value is assigned to the human control material based on a reliable reference method.

REFERENCES

1. Gowans EMS, Hyltoft Petersen P, Blaabjerg O, Hørder M. Analytical goals for the acceptance of common reference intervals for laboratories throughout a geographical area. Scan J Clin Lab Invest 1988; 48: 757-764.

2. Djurhuus MS, Rohold A, Vadstrup S, Hyltoft Petersen P, Uldall A. Reference intervals based on hospitalized 'healthy' patients and medical students in relation to analytical bias for serum potassium. Scand J Clin Lab Invest 1992; 52: 305-312.

3. Uldall A, Glavind-Kristensen S, Bak S. Preparation of fresh frozen human sera for external quality assessment. Scand J Clin Lab Invest 1989; 49: 11-14.

4. Solberg H E. Approved recommendation (1987) on the theory of reference values. Part 5. Statistical treatment of collected reference values: determination of reference limits. J Clin Chem Clin Biochem 1987; 25: 645-656.

5. Gardner MJ, Altman DG. Statistics with confidence - confidence intervals and statistical guidelines. Belfast: BMJ, 1989:

6. Tonks DB. A study of the accuracy and precision of clinical chemistry determinations in 170 Canadian laboratories. Adv Clin Chem 1963; 9: 217-233.

7. Cotlove E, Harris EK, Williams GZ. Biological and analytic components of variation in long-term studies of serum constituents in normal subjects. III. Physiological and

medical implications. Clin Chem 1970; 16: 1028-1032.

8. Barnett RN. Medical significance of laboratory results. Am J Clin Pathol 1968; 50: 671-676.

9. Glick JH. Expression of random analytical error as a percentage of the range of clinical interest. Clin Chem 1976; 22: 475-483.

10. Harris EK. Statistical principles underlying analytic goal-setting in clinical chemistry. Am J Clin Pathol 1979; 72: 374-382.

11. Hultman E, Bergström J. Plasma potassium determination. Scand J Clin Lab Invest 1962; 14: 87-93.

12. Rosa RM, Silva P, Young JB, et al. Adrenergic modulation of extrarenal potassium disposal. New Eng J Med 1980; 302: 431-434.

13. Fraser CG, Cummings ST, Wilkinson SP, et al. Biological variability of 26 clinical chemistry analytes in elderly people. Clin Chem 1989; 35: 783-786.

Correspondence:

Mogens Stig Djurhuus,

Department of Clinical Chemistry, Odense University Hospital,

5000 Odense C, Denmark.