Development of reference limits within the scope of biological effect monitoring. Interpersonal and intrapersonal variation
van Geen, F.

Citation for published version (APA):
van Geen, F. (2000). Development of reference limits within the scope of biological effect monitoring. Interpersonal and intrapersonal variation

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Download date: 22 Dec 2018
2 PERSONAL REFERENCE LIMITS

2.1 INTRODUCTION

Why did Williams et al. (1978) conclude that personal-based reference values are of more value than group-based values?
In this chapter the historical aspect of their conclusion will be considered.

2.2 HISTORICAL REVIEW

In the late sixties Williams et al (1970) demonstrated in 68 healthy subjects, selected after medical evaluation, that:

a. the personal mean concentrations of given blood constituents (collected weekly for ten to twelve weeks) were consistently within the limit of a reference population distribution;
b. the range (by means of personal sd's) of intrapersonal variances of the blood constituents involved was in general smaller than the range (by means of the overall sd of these blood constituents) of the reference population distribution.
These observations have led to interesting studies of the character of individual normal ranges of blood constituents and of their consistency.

Harris et al (1970) introduced the concept of “components of variance” in this type of research. They used a statistical method and study design to be able to estimate the biological components:

\[ S_T^2 = S_B^2 + S_A^2 \]
\[ S_B^2 = S_P^2 + S_I^2 \]

in which
- \( S_T^2 \) = total variance
- \( S_B^2 \) = biological variance
- \( S_A^2 \) = analytical variance
- \( S_P^2 \) = intrapersonal variance
- \( S_I^2 \) = interpersonal variance

They made the assumption that the separate components of variance are additive and independent of mean values. Their major finding was that a chemical test will contribute to individuality, in other words will provide specific information to characterise an individual, only if the combination of intrapersonal and analytic variance components is substantially less than the interpersonal variance.

Cotlove et al (1970) examined the types of variation more precisely. They charted the magnitudes of five types of variations as coefficients of variation. In addition, they calculated the "subject mean" of each particular constituent, which represents the "set point" concentration
of homoeostatic regulation. Not surprisingly, they supported the point that the isolated intrapersonal variance, separated from analytic deviations, measures the extent of fluctuations above and below the set point that is allowed by the subject's homoeostatic mechanism in equilibrium with the internal and external "environment". Subsequently, the isolated interpersonal variance, separated from both intrapersonal and analytic components, reflects differences in homoeostatic set points of different individuals, arising from such factors as genetic characteristics, status after morbidity, diet, physical activity, chronic diseases and age.

The hypothesis developed in the study of Cotlove et al (1970) indicates that a subject mean will be a better discriminating criterion to detect mild states of abnormality in the same individual than a group mean. In addition, the intrapersonal variance itself may also be useful since an impaired regulatory mechanism may manifest itself by an abnormal degree of variation as well as by an abnormal mean concentration.

Young et al (1971) investigated the biological component of variance of nine subjects with fairly uniform demographic characteristics. They expected that the nine subjects would show minimal interpersonal differences; however, in most parameters these individuals showed a purely interpersonal variance that was greater than or as great as the one found among the diverse group of 68 subjects studied earlier (Williams et al, 1970). Young et al (1971) concluded that certain
blood parameters depend more on personal characteristics than on broad demographic factors.

In the 1970s, the above-mentioned authors and others studied the same components of variance and their medical implications in order to explore and develop statistical models suited for long-term studies of healthy individuals. Harris and De Mets (1972) observed that a distribution of single measurements may have any form or shape, depending on the characteristics of the interpersonal and intrapersonal distributions from which it sprang. The shape of the distributions of interpersonal mean values plays a major role, but the distribution of intrapersonal variances is also an important factor. Harris (1974) proposed a numerical index combining interpersonal and intrapersonal variance for use in judging the appropriateness of applying which normal range to apply to an individual measurement regarding some biochemical constituents: a ratio (between the average intrapersonal variance and the interpersonal variance among individual mean values) of 0.6 or lower is considered to support the need for e.g. intrapersonal reference limits instead of cross-sectional reference limits for individual monitoring purposes. Stratifying a sampled population into homogeneous subgroups did increase the magnitude of the index, but it failed to produce a substantial improvement in sensitivity. For this reason, Harris (1976) introduced three statistical time-series models, to use the individual as his own reference: an "overall" model (called Intermediate Model) and two models derived from this overall model: the Random Walk Model and the
Homoeostatic Model. The Intermediate Model postulates regulation towards a set point. The Random Walk Model postulates fluctuation of the biological component in a random manner. The Homoeostatic Model postulates homoeostasis over a period of time. One crucial issue among the three models is the meaning of the values of previous results in testing a new observation, e.g., given the situation of a number of (equispaced) observations over a certain period of time. In chapter 3 a combination of the Random Walk Model and the Homoeostatic Model will be illustrated.

Another issue is the intrapersonal correlations of some serum constituents with each other in healthy persons. Winkel et al (1975) examined the intrasubject correlations among:

a. potassium, calcium and albumin  
b. urea, creatinine and uric acid  
c. aspartate aminotransferase, lactate dehydrogenase and alkaline phosphatase.
Venapunctures were performed on 11 healthy male students at 08.00 h., 11.00 h. and 14.00 h. daily on five different days over approximately a one-month interval. They found from subject to subject different and low correlation coefficients within each combination and, cautiously, they concluded that studying relationships between results of laboratory tests of different serum constituents might yield no meaningful clinical information.

After the development of multichannel analysers and their consequences for long-term analytic variances, Pickup et al (1977) once again studied the problem of cross-sectional population-based reference limits versus personal reference limits. In this study, the subjects were not students, colleagues or patients, but employees of a plant (37 male subjects with 22 weekly blood collections). Pickup et al used the same statistics as in the earlier studies. Their results in determining the appropriateness of population-based reference ranges generally confirmed previous studies (Williams et al, 1970; Harris et al, 1970; Cotlove et al, 1970; Young et al, 1971; Winkel et al, 1975): the usual population-based reference limits were found to be either insensitive or irrelevant to the study of concentrations, i.e. changes over time, within most healthy subjects.

Although Williams et al (1978) were not able to develop new ways of looking at the material, they showed that dividing a population of 1105 healthy subjects into six classes according to age and sex reveals statistically significant differences between the means of many
variables of the different classes. After examining the sensitivity of the ranges of variations within these classes to individual variation, their conclusions about the usefulness of accepted normal ranges confirmed the former studies (Young, 1971, Harris, 1974), indicating personal-based reference values to be of more value compared to group-based reference values.

Harris and Brown (1979) studied the observed changes between two successive measurements of an individual. Using the data described by Pickup et al (1977), they focussed on the individual standard deviations and their frequency distributions. The distributions of all ten serum constituents studied (creatinine, total bilirubin, alkaline phosphatase, calcium, inorganic phosphatase, total protein, albumin, urea, sodium and potassium) appeared to be lognormal. They calculated the coefficients of variation of the individual standard deviation and observed heterogeneity of the individual standard deviations of values for a constituent. After ranking the individual standard deviations, the results showed highly significant differences between the subjects with respect to their intrapersonal variabilities in the concentrations of the blood constituents.

After discussing a statistical way to describe the general pattern of variations over time within a subject and to test the appropriateness of a threshold difference between two serial measurements, Harris and Brown (1979) concluded that the variance heterogeneity (i.e. substantial differences among intrapersonal variances of a blood
quantity examined by means of the coefficient of variation of personal sd's) could be a critical factor in assessing the importance of a change between two successive measurements of an analyte. A specific quantitative change may become statistically and physiologically significant in a subject whose usual biological variation for the analyte is relatively small, but not important in one with large variation. Harris and Brown conjectured that factors which influence personal variances include fluid intake, diet and physical or psychological stress. A very stable or very erratic life style would be expected to display small or large individual variances respectively.

Finally, whichever model was chosen, many investigators computed ranges on the basis of laboratory results already observed in a given subject. Harris et al (1980) and Winkel et al (1975) introduced the terms "subject-specific prediction intervals" and "subject-specific reference intervals": previous laboratory results are used to estimate an interval which will contain the value as measured in a future specimen with a specified probability, subject to the condition that the person is still in the same state of health. Stamm's "critical difference" (1982) indicates the range that covers the great majority (e.g. 95%) of the differences between two values of one parameter obtained in one individual. Costongs (1984) elaborated on this concept, which will be introduced in chapter 3.
2.3 DISCUSSION AND CONCLUSIONS

In accordance with Harris (1974) we assume that the issue concerning the choice between group-based reference values and personal-based reference values is determined by the index between the interpersonal and intrapersonal variances of a quantity; if the intrapersonal variance of a blood constituent is substantially less than the interpersonal variance, then the conventional limits based on a single sample distribution of the same parameter in a reference population will be insensitive in detecting early departure from a subject's normal range of variation.

In assessing the importance of a change between two successive measurements of a blood quantity within a subject, the variance heterogeneity could be a critical factor. But how does the physician know that observed individual variations are distributed at random? How does the physician know that a quantitative change is physiologically significant in a subject whose biological variation for the analyte is relatively small or that is not important in a particular subject with a large random variation?

Moreover, Harris et al (1970) assumed that the separate components of variance of a blood constituent within a single person are additive and independent of the mean values, whereas the observed personal mean was considered to be the best estimate of the homoeostatic set point. It is very difficult to define the term set point: the term is used to indicate the point around which the "true" values of a blood
constituent will vary. The set point would be genetically determined. However, a homoeostatic mechanism is physiologically characterised by three features: the homoeostatic set point, the extent to which the homoeostatic mechanism conforms to its set point, and determinants (age, illness, lifestyle and workload). There is uncertainty about what is inherited: the set point and/or the strength of response of the system involved (Murphy and Trojak, 1983).
The homoeostatic mechanism of a blood constituent may vary in amplitude and in set point. The observed intrapersonal variation is an expression of biological responses, which depends on:
a. personal kinetic and dynamic processes, accounting for e.g. diurnal rhythmic changes and connected interrelationships between organ systems,
b. the type and impact of external factors possibly influencing the variation.

The observed personal mean over a period of time is determined by the given period of time of observation. The observed personal means of blood constituents may be affected by a temporary abnormal degree of variation, for instance due to a momentary out of the ordinary life style or short-term exposure to a chemical agent: in that case the observed personal mean is a "temporary phenotypic value". For this reason, it is questionable whether each observed personal mean can be regarded as the best estimate of the homoeostatic set point of a blood constituent. A worker will usually become employed somewhere in the second or third decennium of his/her life. Before entering the workforce there will exist, in a worker, under optimal environmental
conditions - at least theoretically - a basic level of functioning of the homoeostatic mechanism of a blood constituent: his ideal phenotypic level, the result of heredity and of the life/work history. When this worker experiences periods of erratic life style, then there will be, somewhere between his "ideal" phenotypic level and the erratic personal means at that time, another phenotypic level: a level based on periods of living according to social acceptability and social habits.

So, the point or the period of time of observation is very critical to an observed personal mean and variance. If the physician interprets separate values by means of cross-sectional reference limits only, he/she is not able to interpret personal means and variances in terms of 'normal' or 'abnormal'. So, during BEM, in order to interpret an observed personal mean value and variance, the occupational physician should have group-based reference limits of personal means and of personal variances instead of cross-sectional reference limits.

*An example:*

Mr. C., born in 1938, consumed anti-hypersensitive drugs and had high alcohol consumption. In the second month of blood sampling he was strongly advised to stop alcohol consumption because of the risk of developing alcohol-induced hepatitis. Only from the eleventh to the fifteenth month did he reduce his alcohol intake, after which his consumption of alcohol increased again. This story can be summarised and illustrated by using the measurements of his ALAT activity (figure 1).
The example demonstrates the importance of the point in time or period of observation: every six months the pattern differed. A changing pattern may indicate a changing personal mean value and/or personal sd value e.g. based on a trend. If Mr. C. were to be followed by means of mean values and sd values of his ALAT-activity, it is not clear when it would be appropriate to conclude an abnormality in these values.