A Practical Approach to Quantitate Hepatic Excretory Function

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A statistical comparison of different BSP tests was carried out in normal subjects and in patients with various degrees of chronic liver damage. Only the logarithm of the BSP retention correlated linearly with the physiologically more meaningful determination of the maximal excretory capacity of the liver (BSP Tm, Wheele's method). A double logarithmic transformation was required to correlate the second exponential component of the BSP plasma disappearance curve (k2) with the BSP Tm. When the limitations of these methods are kept in mind, the observed statistical relationships can be used to express hepatic functional deterioration in more physiological terms.

In patients with pulmonary or renal disease it is an established procedure to use quantitative function tests to follow the progression of the disease and/or to assess the effects of various forms of treatment. By contrast, analogous approaches to studying patients with liver diseases have been used only rarely. The need to develop quantitative tests of hepatic function has not been pressing because specific and effective therapy has not been available. Recently, however, clinical trials have accumulated evidence to suggest that chronic active liver disease may be successfully treated with corticosteroid hormones (1–3). Consequently quantitative clinical tests to measure partial hepatic functions have become more desirable.

With the presently available sulfobromophthalein—or BSP—tests—as in many other areas of medicine—there is an inverse relationship between simplicity of the procedures and specificity of the information they can give (Table 1). Indeed, only the measurement of the hepatic transport maximum for BSP can truly be considered to represent a quantitative expression of hepatic excretory function (4). In practice, the test based on Wheeler's method is cumbersome and time-consuming and, therefore, seems ill-suited for the clinical routine. By contrast, the conventional BSP retention test is widely used and generally accepted. It is technically simple and empirically quite sensitive for the detection of liver disease (5). Consideration

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Table 1
BSP Tests Used to Assess Hepatic Function. "Specificity" Implies That the Information Provided by the Test Expresses Changes in Excretory Function Quantitatively

| Test                              | Simplicity of procedure | "Specificity" of information |
|-----------------------------------|-------------------------|-----------------------------|
| 1 BSP retention (5)               | ++                      | −                           |
| 2 BSP plasma disappearance curve (6-8) | +                      | +                           |
| 3 BSP transport maximum (4)       | −                       | ++                          |

of its physiological rationale, however, illustrates that the results must be interpreted with caution.

The concentration of BSP in the plasma used for the 45-min BSP retention (C15t) may be calculated as follows:

\[ C_{15t} = \frac{BSP_{\text{inj.}} - BSP_{\text{excr.}}}{VD} \]

The equation shows that \( C_{15t} \) is directly proportional to the difference of the amounts of BSP injected (\( BSP_{\text{inj.}} \)) and excreted (\( BSP_{\text{excr.}} \)) and inversely proportional to the volume of distribution of BSP (\( VD \)). The injected quantity of BSP is standardized to 5 mg/kg body wt. Only the proportion excreted by the liver is related to hepatic function. Since, however, the concentration of BSP offered to the liver varies continuously throughout the test, it cannot be expected that the amount of BSP excreted during 45 min bears any simple relationship to the excretory capacity of the liver. The well-established complexities of hepatic handling of BSP further complicate the problem: Apart from BSP binding to plasma and intrahepatic acceptor proteins, at least conjugation and reflux into the plasma have to be considered as well. The volume of distribution appearing in the denominator is larger than the plasma volume, and its relation to disease processes is not adequately defined. These aspects, therefore, limit interpretation of the results to an empirical and statistical basis.

The third test used to assess liver function is an analysis of the BSP plasma disappearance curve. If frequent samples are taken, the curve may often be described as a double exponential function (6, 7). Despite the formulation of kinetic models (8), the physiological basis for these curves has remained insufficiently understood.

Consequently, studies in our department were directed to further evaluate the BSP retention and the BSP plasma disappearance curve (5, 9). In a group of patients with various liver diseases and in normal control subjects, the three tests have been carried out in one session. A comparison of the results revealed that the simple tests may be interpreted in terms of specific partial functions.

The BSP disappearance curves were measured after the intravenous injection of 5 mg/kg of BSP within 30 sec. Blood samples were obtained at 3, 5, 7, 10, 15, 20, 25, 30, 35, 40, and 45 min after the beginning of the injection. The last sample was used to calculate BSP retention assuming an initial concentration of 10 mg/100 ml.

The BSP \( Tm \) was determined indirectly with the two-infusion method as described by Preisig et al. (10). The principles of this method are based on the idea,
that with the chosen experimental conditions, the intravenously infused BSP is either distributed within its volume of distribution—plasma volume (PV) and hepatic storage compartment (S)—or excreted at the rate (Tm) which is maximal for the liver to be studied (4).

The distribution of BSP can be calculated as product of the rate of change in plasma concentration (ΔC/Δt) and the volume of distribution (PV + S). Consequently, the equation may be written as:

\[
\text{Infusion} = Tm + \frac{\Delta C}{\Delta t} \cdot (PV + S).
\]

As only the rate of infusion and the plasma concentrations can be measured there remain two unknowns (Tm and S). Two different infusions, therefore, have to be administered in order to produce two equations with two unknowns, which then can be solved. The practical application of the test requires consideration of many details which have been discussed elsewhere (4, 11).

The first finding of our comparative analysis consisted of the empirical fact that only the logarithms of the BSP-retention were linearly correlated with the excretory capacity of the liver as revealed by the BSP Tm (Fig. 1). This type of relationship implies that the degree of abnormality revealed by the BSP retention has no direct proportionality to the functional deterioration of a diseased liver. The higher the measured BSP retention, the more sensitive it is in revealing changes of excretory function. This observation led to a definition of new BSP retention units. They were constructed to express linearly functional deterioration of the excretory system and can be read directly from the nomogram of Fig. 2. The normal mean value was regarded as zero retention. The range up to 1.0 retention unit was taken as normal, whereas the higher values correspond to directly proportional decreases in the excretory capacity of the liver for BSP. Application of such retention units to clinical problems should always take into account, however, that they were de-

![Figure 1](image-url)

**Fig. 1.** The correlation of BSP retention and BSP Tm has to be semilogarithmic to yield a straight regression line. The points refer to control persons, the triangles to patients with cirrhosis of the liver, and the crosses to patients with various other liver diseases. (Reproduced with the kind permission of the *Schweiz. Med. Wochereschr.*)
fined on a statistical and not a pathophysiologically recognized relationship. Their justification, therefore, remains empirical.

A similar analysis was carried out with the BSP plasma disappearance curve. Its most important finding consisted in the close correlation between the logarithms of the second component \( (k_2) \) of the disappearance curve (Fig. 3) and the BSP transport maximum, suggesting that \( k_2 \) is mainly determined by the excretory capacity of the liver (Fig. 4). In support of this assumption there was no significant relationship between \( k_2 \) and hepatic blood flow \( (r = -0.08) \) as measured with the

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**Fig. 2.** Nomogram to show the relationship between the conventional 45-min BSP retention (in \%) and the newly defined arbitrary BSP retention units, which express linearly hepatic functional deterioration. The normal range is below 1.0 retention unit. (Reproduced with the kind permission of the Schweiz. Med. Wochenschr.).

**Fig. 3.** \( k_2 \) as defined in our laboratory, depends on BSP concentrations between 30 and 45 min after the injection of 5 mg/kg BSP. For comparison, also the initial part of the plasma disappearance curve is shown.
ICG-infusion and extraction technique (12). Physiologically, \( k_2 \) could be explained on the basis of a two-compartment model, where, in addition, the actual BSP plasma concentrations had to be taken into account. Even though the details, especially the mathematical derivation, are described elsewhere (9), the model may be regarded as an adequate basis to justify the use of \( k_2 \) for estimations of BSP TM.

In practice, this test requires only four determinations of BSP plasma concentrations, 30, 35, 40, and 45 min after the injection of BSP. The value of \( k_2 \) is calculated from the graphically read half-life \( T_{1/2} \) provided three of the four points can be accurately fitted to a straight line \( (k_2 = 0.693/T_{1/2}) \). When this condition is not fulfilled, the resulting \( k_2 \) is inaccurate and should not be used. In our experience, this difficulty occurred in 39% of normal subjects but only in 10% of patients with impaired function. Consequently this procedure is more suitable to assess degrees of abnormality than to define a normal population. The values for \( k_2 \) obtained with this method, can be converted to "estimated" BSP TM values with the aid of another nomogram, depicted in Fig. 5. The specific conditions suggested for the determination of \( k_2 \) were found by trial and error. The failures to get a straight line between 30 and 45 min after injection of BSP in a high percentage of control subjects were due to the relatively rapid disappearance of BSP from the blood leading to low plasma concentrations which were difficult to measure accurately enough. In patients with impaired liver function, a hump in the curve occasionally rendered \( k_2 \) inaccurate. Severe cholestasis or the Dubin–Johnson syndrome usually were associated with a \( k_2 \) approaching zero. The secondary rise in plasma BSP concentration often seen in these cases generally occurred after 45 min and consequently did not interfere with the assessment of \( k_2 \).

If further studies on a larger scale confirm the results obtained in our laboratory, the use of BSP \( k_2 \) and of BSP-retention units should be valuable in the follow-up of patients treated for chronic liver disease. Both tests are simple enough for the clinical routine and give information about quantitative aspects of the excretory function of the liver. Because of its better established physiological basis, the BSP \( k_2 \) is directly applicable to the individual patient and, therefore, may be preferred.

![Image](image.png)

**Fig. 4.** The correlation between BSP \( k_2 \) and TM is curvilinear and gives a straight line only if a double logarithmic plot is used. The open circles represent control persons, the closed circles symbolize patients with histologically proven cirrhosis of the liver, and the crosses are derived from cases representing various chronic liver diseases.
Fig. 5. The nomogram for the conversion of $k_2$ to “estimated” BSP $Tm$ is based on the regression line shown in Fig. 4 and on a two-compartment model exhibiting saturation kinetics at the excretory step. It allows estimations of the BSP $Tm$ on the basis of $k_2$, provided the experimental findings are good enough for the calculation of $k_2$.

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