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Evaluation of Pharmacokinetic Methods Used to Estimate Caffeine Clearance and Comparison With a Bayesian Forecasting Method

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Summary:

Simplified pharmacokinetic methods have been used to estimate caffeine clearance in subjects with liver disease. There is a need to have a reliable, easy to implement method for research and possible clinical use. This study evaluates the use of Bayesian pharmacokinetic forecasting techniques to estimate caffeine clearance and compares its performance to other published methods. Commonly used published methods include the two-concentration overnight salivary clearance method (*Jost* method) and a method that samples caffeine concentrations over a 4-hour time period(*Nagel* method). Both have been used in studies incorporating serial measurements of caffeine clearance to predict clinical outcomes in subjects with liver disease, but these approaches have not been proven useful. However, neither method has been formally evaluated for accuracy in estimating caffeine clearance in subjects with cirrhosis. The performance of the *Jost, Nagel*, and Bayesian methods was compared to a*Gold Standard* method that accurately measured caffeine clearance in healthy subjects and subjects with cirrhosis using an intravenous infusion of stable isotope-labeled caffeine. The Bayesian method, even when only one measured concentration of caffeine was used, was more accurate, better correlated to the *Gold Standard* method, and had less intraindividual variation than the two previously published methods. Before the idea of using serial measurements of caffeine clearance for clinical usefulness is rejected, a reevaluation using methods of estimating caffeine clearance that are more accurate than previous paradigms is needed.

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With the advent of liver transplantation, more precise measures of hepatic function (than the Child-Turcotte-Pugh score [1]) have been sought to optimize the use of this expensive therapy. The measurement of caffeine clearance has been proposed as a tool to assess hepatic function (2-4). However, its usefulness as a clinical tool is limited. Limitations include difficulty in implementing such a cumbersome measure in clinical practice, the changes in caffeine clearance with dose (5,6), the influence on caffeine metabolism by environmental factors (7-10), and perhaps even genetic differences (11,12). These factors result in a large interindividual variation in caffeine clearance in healthy subjects and patients with liver disease (13-16).

Outline

To improve the ease of use in measuring caffeine clearance, simple pharmacokinetic methods of estimating caffeine clearance have been put forward (17-19). To detect a significant change in hepatic function in the setting of wide intersubject variation in caffeine clearance, it has been suggested that caffeine clearance be measured in the same individual on multiple occasions. In this way, an individual's rate of decline in hepatic function will be reflected by the decrease in that individual's caffeine clearance measurements. Such a continuous measure of decline in hepatic function may give a more precise estimate of the optimal time for transplantation, and, once transplanted, may predict rejection at an earlier time than current approaches. Currently, such decisions are often based on the use of the arbitrary Child-Turcotte-Pugh score (20). However, two studies using serial measurements of caffeine clearance in patients with liver disease did not show any benefit in the prediction of outcomes (21,22). These studies can be criticized for the infrequency of measuring caffeine clearance and for the use of methods to estimate caffeine clearance that have not been validated as accurate or reproducible in the group of subjects that is of clinical interest.

One method for estimating caffeine clearance that has often been used for research purposes in subjects with liver dysfunction and was used in one of the serial measurement studies (22) is the overnight salivary (or plasma) caffeine clearance method first advocated by Jost et al (19). This method entails the use of an oral dose of caffeine, usually taken in the afternoon, and then two salivary or serum samples are collected-one before sleep and the other the next morning (i.e., a time span between samples of 10 to 12 hours). No intervening consumption of caffeine is allowed. There are slight variations used in the literature, but the essential elements remain, i.e., the actual dose is not important; the two samples collected are often collected in a time frame that is less than one half-life of the caffeine seen in subjects with cirrhosis; the slope of the caffeine decline is calculated from just these two caffeine concentrations and multiplied by a population value for the volume of distribution (V), which gives a one-compartment model estimation of caffeine clearance. The major concern is that the optimal approach to pharmacokinetic parameter estimation usually requires samples to be collected over a period of at least three half-lives so that the actual slope in the decline in concentrations can be assessed accurately. Because the half-life of caffeine in subjects with cirrhosis is often prolonged to 20 hours or more (15,16,23-25), a sampling protocol over 8 to 12 hours may lead to considerable error in estimation of the slope. In addition, there is some controversy regarding the use of a single population estimate for V because there is evidence that V changes in patients with cirrhosis (24,26) and particularly when ascites is present (5,25).

The other study that uses serial measures of caffeine clearance in patients with liver disease, proposed by Nagel and coworkers, used a different method of estimating caffeine clearance (21). In this case, an intravenous dose of caffeine was administered and a sampling paradigm over 4 hours was used. No validation of this method appears in the literature.

The use of Bayesian statistical methods in the estimation of pharmacokinetic parameters is now well established (27-29). This method has a number of potential advantages including the possibility that it may compensate for the short sampling paradigms that, for clinical usefulness, will always have to be used in subjects with cirrhosis, and that only one estimation of caffeine concentration may be needed. We have published data previously on the clearance of caffeine using a stable isotope-labeled caffeine technique and noncompartmental pharmacokinetic data analysis (14,16). The clearance of caffeine was measured in healthy controls and subjects with cirrhosis. This data set presents the opportunity to evaluate the accuracy and precision of the two methods for estimating caffeine clearance described earlier and to compare their performance to Bayesian forecasting.

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MATERIALS AND METHODS

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Experimental Protocol

Details of the experimental protocols have been described previously (14,16). All procedures were performed with informed consent as approved by the Committee on Human Research, University of California, San Francisco, U.S.A. In one study, 12 healthy controls were admitted to the General Clinical Research Center at San Francisco General Hospital and had caffeine clearance (CL) measured on two separate occasions. A subset of this group (eight subjects) returned approximately 1 week after the first admission for a third caffeine CL estimation. Caffeine clearance was quantified by administering to the subjects 25 mg of intravenous stable isotope-labeled caffeine ([2-^{13}C,1,3-$^{15}N_2$] caffeine); blood sampled was at 5, 15, 30, 45 minutes, and 1, 2, 3, 5, 8, 12, and 24 hours after injection for the measurement of labeled caffeine. A one- or two-compartment model using extended least squares regression (MKMODEL) was used to approximate the decline in plasma concentrations of the isotope-labeled caffeine. Area under the plasma concentration-time curve(AUC) was computed by the log-linear trapezoidal rule with the terminal area calculated by the last measured labeled caffeine concentration divided by the elimination rate constant, which was estimated by the regression analysis. Clearance was calculated as DOSE/AUC. This method of caffeine clearance estimation will be called our Gold Standard method.

In a second study, 11 subjects with cirrhosis were enrolled for the measurement of caffeine clearance. Eight of these subjects returned 1 week later for a second estimation of caffeine clearance (a total of 19 estimations). Most had cirrhosis caused by alcohol or hepatitis B or C. One had secondary biliary cirrhosis. Their Child-Turcotte-Pugh score ranged from 5 to 12 (mean, 8.8); 8 of the 11 subjects would be classified as Child's B. Caffeine clearance was measured using the same protocol as for the healthy controls except that the sampling continued for more than 24 hours, every 12 hours for a total of 96 hours. Thus, a total of 32 clearance measurements for healthy subjects and 19 measurements of clearance for subjects with cirrhosis could be used to evaluate the performance of the proposed simplified pharmacokinetic methods of estimating caffeine clearance. The average half-life as calculated by the *Gold Standard* method was 4.2 hours in the healthy subjects and 21 hours in the subjects with cirrhosis.

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Analytical Methods

The purification and assay procedure of the source of the stable isotope-labeled caffeine are described in a previous paper (6). Isotope-labeled caffeine was measured by gas chromatography-mass spectrometry. The coefficient of variation at 10 ng/ml was 15%. This value was used as the lowest concentration of measurable caffeine.

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The Overnight Caffeine Clearance of *Jost* Method

The differences between our study and the method published by Jost were that the dose of isotope caffeine was administered intravenously in the morning (instead of two oral doses in the afternoon) and the two plasma(instead of salivary) concentrations selected for the calculation of clearance usually were concentrations measured at 12 and 24 hours after the caffeine dosing. In the group of healthy subjects, some of the subjects did not have a measurable level of isotope caffeine at 24 hours after the dose; therefore, in these cases the 2- and 10- or 12-hour samples were used. By 2 hours, the distribution phase that follows intravenous caffeine is over (14). The use of an intravenous dose of caffeine instead of oral caffeine dosing is of no importance as the bioavailability of caffeine is 100% (30). Calculation of clearance was performed identically to the published method and expressed as a function of body weight. This method is a simplified version of the least squares regression method that is used commonly in traditional pharmacokinetic parameter estimation.

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The 4 Hour or *Nagel* Method

The method used by Nagel et al (21) involves sampling plasma for the measurement of caffeine concentrations at 0.5, 1, 2, 3, and 4 hours after a dose of caffeine. In the protocol for the measurement of the stable isotope-labeled caffeine clearance, there was no collection of a plasma sample at 4 hours, therefore, the 0.5-, 1-, 2-, 3-, and 5-hour isotope caffeine concentrations were used. A linear least squares method using these five concentrations is used to estimate the slope of the caffeine concentration decline.

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Bayesian Estimation of Caffeine Clearance

A computer program designed by Abbott Diagnostics (Irving, TX, U.S.A.) that runs on an IBM (White Plains, NY, U.S.A.) compatible microcomputer was used for the calculations (ABBOTTBASE PK Systems, version 1.10). The Bayesian method for the estimation of pharmacokinetic parameters requires an a priori estimate of the average population values for volume of distribution (V) and clearance and an estimate of the variance of these population parameters. The population pharmacokinetic parameters are then compared to pharmacokinetic parameters generated by a least squares regression method for the individual subject based on that subject's measured caffeine concentrations. The resulting parameters are a hybrid of population and individual parameters weighted by the variance of the population parameters and the experimental error that occurs in sampling, and with the use of a least squares regression method based on only one or two caffeine concentrations.

The first step in developing the Bayesian method was to obtain adequate population pharmacokinetic parameter values for healthy subjects and subjects with compensated and decompensated cirrhosis. The literature was searched for suitable studies that could form the basis for population pharmacokinetic parameter estimates. Only studies using noncompartmental pharmacokinetic methods to estimate these parameters were used and an average, taken across all suitable studies, was calculated. For healthy subjects, a clearance value of 0.114 l/hr·kg with an average coefficient of variation (CV) 41%, and a V value of 0.63 l/kg with an average CV 19.9%, were used based on a number of studies from the literature (5,10,13,15,23,31-34). Two subjects could be classified as patients with compensated cirrhosis and the others were classified as patients with decompensated cirrhosis. Compensated cirrhosis is defined as a Child-Turcotte-Pugh score of 7 or less, whereas higher scores are classified as decompensated cirrhosis. For subjects with cirrhosis, only three published studies fulfilled the criteria and only two of these measured caffeine pharmacokinetic parameters in decompensated and compensated cirrhosis (5,15,23). For compensated cirrhosis, a clearance value of 0.08 l/hr·kg (average CV, 51%) and for V, a value of 0.46 l/kg (average CV, 35%) was used; for decompensated cirrhosis, the clearance value used was 0.023 l/hr·kg(average CV, 45%) and V was 0.59 l/kg (average CV, 21%). In many other studies using one-compartment model pharmacokinetic equations to calculate caffeine clearance, the CV for this parameter in subjects with cirrhosis was much higher than the overall average CV in the three studies chosen (19,35-37). Therefore, the Bayesian estimation for the group with cirrhosis was repeated using a higher value for the variance of caffeine clearance. The value used was a doubling of the CV for decompensated cirrhosis, i.e., a CV of 90%. The use of this higher CV for the population value of clearance also was evaluated in the healthy subjects for the one-concentration Bayesian forecasting method.

The same plasma concentrations used for the *Jost* method were used in the Bayesian forecaster. In addition, a further Bayesian estimation was performed using a single plasma concentration. In this case, only the 24-hour concentration was used (or, in the healthy subjects, the 12-hr concentration when a 24-hour level was below the lower limit of reliable estimation). The exact dose and time the infusion of isotope-labeled caffeine was given is required by the Bayesian forecaster.

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Least Squares Regression Method to Estimate Caffeine Clearance

The ABBOTTBASE PK System software (Abbott) also has the ability to estimate pharmacokinetic parameters using linear least squares regression. This method involves the use of linear regression to estimate the slope of the decline in caffeine concentrations, and this slope is used to estimate clearance and V using standard one-compartmental pharmacokinetic equations. This is very similar to the *Jost* method except that, with knowledge of the dose used, direct estimation of the subject's V can be made and, therefore, this will probably give a better estimation of clearance. The same two caffeine concentrations used in the *Jost* and Bayesian methods were also used here to estimate caffeine clearance.

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Statistical Analysis

The correlations between various simplified estimations of clearance and *Gold Standard* clearance values were performed by linear regression. The coefficient of determination (r^2) was corrected for the degrees of freedom. Because a high value for the coefficient does not necessarily reflect accuracy between two methods, the analysis suggested by Sheiner and Beal was also performed (38). The bias or mean error (ME) and the precision or mean square error (MSE) were calculated for the difference between clearance measured by the *Gold Standard* method and clearance estimated by the other surrogate methods. These data and the clearance values for each method were tested for normality using the Shapiro-Wilk test (39) and the data were largely nonnormal. This latter finding indicated that instead of using mean error and mean square error, the median error and the median square error should be used. The data were ranked and a two-factor analysis of variance (ANOVA) in association with a corresponding Tukey multiple comparison test was used on the ranked data for hypothesis testing. The accuracy of prediction by the simplified methods was also evaluated by assessing each method's ability to reach 10% or 20% of the clearance value calculated by the *Gold Standard* method.

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RESULTS

Table 1 displays the calculated clearance values for each method. For the subjects with cirrhosis, clearance values estimated by the *Jost* and *Nagel* methods were significantly different from the *Gold Standard* clearance values. In healthy subjects who had the measurement of clearance performed on two (12 subjects) or three occasions (8 subjects), the average intraindividual CV of clearance was 17% for the *Gold Standard* method, 13% for the Bayesian methods (one or two concentrations), 15% for the *Jost* method, and 22% for the*Nagel* method. In the subjects with cirrhosis who had the measurement of clearance performed on two occasions (8 subjects), the average intraindividual CV of clearance was 18% for the *Gold Standard* method, 24% for the Bayesian methods, 26% for the *Jost* method, and 27% for the *Nagel* method. All estimates were significantly correlated to the *Gold Standard* clearance values, but the correlations for the *Jost* method in both groups of subjects and the *Nagel* method in subjects with cirrhosis were not as close as the one- or two-concentration Bayesian methods (see Table 2 and Figures 1 and 2). The Bayesian methods using the original population CV (i.e., 45%) for clearance estimated the clearance poorly in just one subject with cirrhosis (data not shown). This outlier explains the much lower coefficients of determination using this particular population parameter for subjects with cirrhosis.


Table 1


Table 2

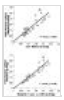
Fig. 1

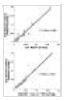
Fig. 2

The median error analysis demonstrated that the *Nagel* method had the most bias in the estimation of caffeine clearance in healthy subjects and subjects with cirrhosis (Table 3). The*Jost* method also had a significantly higher median error than the Bayesian methods in subjects with cirrhosis. The median square errors analysis indicated that the *Jost* and *Nagel* methods had the least precision in the estimation of clearance in healthy subjects and subjects with cirrhosis (Table 4). Another way of expressing these results is to assess each method's ability to come within an arbitrary target range of the *Gold Standard* method (Table 5). Again, the *Jost* and*Nagel* methods were the worst-performing simplified methods, especially in subjects with cirrhosis. In this group, the Bayesian methods had far superior prediction rates.


Table 3


Table 4


Table 5

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DISCUSSION

This study compares a number of simplified methods that could be used to estimate caffeine clearance with a caffeine clearance measured by the traditional method of pharmacokinetic parameter estimation. The traditional method involves the use of an intravenous injection of a stable isotope-labeled caffeine, sampling of plasma to measure caffeine concentrations over a period of at least three half-lives (i.e., for healthy subjects 12 samplings over 24 hours, for subjects with cirrhosis 18 samplings over 96 hours), and the use of noncompartmental pharmacokinetic methods to estimate clearance.

For research purposes, it is important that any simplified method used to estimate the parameter of interest is accurate; otherwise, new findings would have to be questioned and studies repeated. For clinical purposes, where a method is to be used for trend analysis, accuracy is not as important as is the closeness of the correlation to the parameter of interest and the necessity to have a small intraindividual variation, especially if the simplified method is to be used on multiple occasions over time in the same individual. However, it is likely that the least accurate or least precise method will have the worst correlation coefficient and the largest intraindividual variation. Therefore, if simplified methods are to be used in this setting, they must be validated before conclusions are reached regarding their clinical usefulness. This validation must include an assessment of accuracy and intraindividual variation. In our study, it was shown that the least accurate methods, namely the *Nagel* and *Jost* methods, had the lowest correlation coefficients to caffeine clearance in subjects with cirrhosis and the largest intraindividual variation. Therefore, any conclusion that serial measures of caffeine clearance based on the*Nagel* or *Jost* methods have nothing to offer clinical hepatology may be premature (21,22).

The most frequently used method to measure caffeine clearance in liver disease for research and potential clinical purposes is the overnight caffeine clearance method, or *Jost* method (2,3,19,22,25). In our analysis, this was the second worst method for estimating caffeine clearance. The true clearance value was significantly under-estimated by an average of 13% in the subjects with cirrhosis (Table 1) and this method was significantly worse than the two-concentration Bayesian method (Table 3). Its correlation to the values measured by the*Gold Standard* method in both groups of subjects was not as good as the Bayesian methods (Table 2, Figs. 1 and 2). There was a lower precision in healthy controls and subjects with cirrhosis compared to Bayesian approaches (Table 4), and the ability of the method to reach target ranges around the *Gold Standard* clearance value was poor (Table 5). Bayesian methods in this latter comparison outperformed the *Jost* approach in subjects with cirrhosis, reaching arbitary targets of accuracy at far superior rates. In addition, the average CV for two estimations of caffeine clearance in the same subject with cirrhosis was higher with the *Jost* technique than the CV determined by the *Gold Standard* method. The use of the*Jost* method on three occasions over a period of 30 days in seven subjects with cirrhosis could not predict which patient would survive surgery (22). In view of the findings in our study and the small numbers of patients with cirrhosis enrolled, such a result is not unexpected.

The major problems with the *Jost* method are the short time span between sampling times with respect to the half-life of caffeine in subjects with cirrhosis and the use of an average population value for V. The least squares method, which is very similar to the *Jost* approach except that it calculates V directly, was superior and close to the performance of the Bayesian methods. The performance of the *Jost* method in sick Child's C patients with cirrhosis who often have very long caffeine half-lives (23-25) and who have distribution volumes that differ from the population average (5,25) would probably be much worse. In addition, the use of salivary concentrations is expected to increase intrasubject variability. This is because there is a wide range of possible values for the salivary/plasma ratios in subjects with cirrhosis (25). Whereas reproducibility of the method (using salivary concentrations) was assessed in healthy controls (19), this was not done for subjects with cirrhosis. Only on one occasion has the validity of the*Jost* method been assessed, and in this case the *Jost* method was compared to another one-compartment method of pharmacokinetic parameter estimation with seven sampling points over a period of 30 hours (25). There was more than a two-fold difference in the mean estimate for the clearance of caffeine, although no statistical differences were seen (because of the large variation and small numbers of subjects). Although a moderately close correlation could be demonstrated between the estimates of clearance from both methods ($r^2 = 0.66$,$p = 0.0005$), close correlation of two sets of data has little to do with accuracy (38). The findings of our study suggest that the *Jost* technique is too inaccurate to assess caffeine clearance in subjects with cirrhosis for research purposes.

The Bayesian approach to pharmacokinetic estimation tries to use the maximum amount of knowledge concerning the disposition of the drug in question, namely, the use of information from the literature (i.e., population parameter averages for the group of subjects of interest) and those data that can be obtained from the individual of interest (i.e., height, weight, sex, renal function, dose, sampling times, and concentrations). This "maximum of information" method shows its real worth when one compares estimation of caffeine clearance to the use of only one concentration of caffeine with two concentrations used either with the Bayesian approach or the *Jost* method. The use of just one concentration 24 hours after the dose (on occasion, 12 hours in the healthy controls) was very similar to the performance of the two-concentration Bayesian method and superior to the *Jost* procedure.

The use of the higher variance estimate for the population clearance value in the Bayesian models (i.e., Bayesian one- or two-concentrations; CV, 90%) improved the performance of the Bayesian method for subjects with cirrhosis. One of the main problems of the performance in the Bayesian method with a lower CV was a subject with secondary biliary cirrhosis who had a preserved ability to metabolize caffeine. This subject's value for caffeine clearance was in the same range as the healthy subjects. Preservation of metabolic function in patients with biliary cirrhosis compared to other types of cirrhosis has been documented previously (17,40,41). Based on the protocol of this study, the subject was analyzed using the decompensated cirrhosis population parameters because her Child-Turcotte-Pugh score (adjusted for elevated bilirubin levels [42]) put her in the Child's B group. As a result, the original Bayesian population parameters were too narrow, and increasing the variance of the population clearance parameter allowed closer approximation of the clearance value for this subject (Table 2) and improved the accuracy of prediction for many of the other subjects (Table 5). This improvement in accuracy may also have benefits in the estimation of caffeine clearance in sick Child's C patients who have very prolonged half-lives and very low values for the clearance of caffeine. Increasing the CV of the population clearance parameter for the control group made very little difference.

Another advantage of the Bayesian method is that in the occasional subject with a prolonged half-life of caffeine there is very little change in plasma caffeine concentrations overnight and, with measurement error, the morning level can be as high or higher than the level measured the previous evening. In this case, the *Jost* or least squares methods cannot be used. One subject in this study had such data; his caffeine concentration 12 hours after the dose was 423 ng/ml and after 24 hours was 469 ng/ml. This subject had the longest half-life in the study (47 hours). For this study's purpose, a different set of concentrations (the 5- and 24-hour concentrations) was chosen so that the *Jost* and least squares methods could be used, but when the clearance using the original 12 and 24-hour concentrations was reestimated, the Bayesian estimation of caffeine clearance was 0.0084 l/hr·kg compared to the *Gold Standard* value of 0.0092 l/hr·kg. For the one-concentration Bayesian method, the clearance was estimated to be 0.0086 l/hr·kg.

The main advantages of the *Jost* method over the Bayesian method are that the exact dose of caffeine is not required to be known, past consumption of caffeine can be ignored, and the computation of clearance is simple. The advantages in the use of a one-concentration Bayesian method are that it is more accurate, has a lower intraindividual variation than the*Jost* method, and is much easier to perform from the subject's point of view because only one concentration is required the day after the dose of caffeine has been given. With both methods, there can be no intervening caffeine consumption. The disadvantages of the Bayesian method are that it is more difficult to perform the calculation and requires a computer, the exact dose of caffeine given must be known, and the effect of prior consumption of caffeine on the caffeine concentration has to be taken into account. Whereas the first two disadvantages can be overcome easily, the third problem will require caffeine abstinence before the test, sometimes several days earlier for subjects with very prolonged half-lives of caffeine. This problem can be dealt with if three concentrations are measured-one before and two after the test dose of caffeine. The effect of the prior consumption of caffeine, reflected in the caffeine concentration immediately before the test dose of caffeine, can then be factored out by calculating the half-life of this initial caffeine concentration in the subject from least squares regression of the two concentrations after the dose.

Nagel et al estimated caffeine clearance serially in subjects after liver transplantation (21). They used a pharmacokinetic technique that involved taking five concentrations over just a 4-hour time span as described earlier. The subjects in the *Nagel* study had variable clearances and in the group with decompensated cirrhosis, clearance averaged 0.0344 ± 0.02 l/hr·kg, which is lower than the average clearance value for the subjects with cirrhosis in the current study (see Table 1). Thus, the half-life of caffeine would have been even longer in the *Nagel* subjects than in ours. The *Nagel* method would have difficulty in characterizing the slope of the decline in plasma caffeine concentrations because 4 hours is insufficient time to see much of a change in the caffeine concentration. It is not surprising that this group of investigators did not see any correlation between caffeine clearance and clinical course. It should be noted that our use of a 5-hour sample rather than a 4-hour level to compare against the *Gold Standard* makes the *Nagel* method look better than it really is; the use of caffeine concentrations to 3 hours after the dose had even worse results (data not shown). This method overestimates the true caffeine clearance by 25% in cirrhotic subjects (Table 3) and is significantly different from clearance values measured by the *Gold Standard* method (Table 1). The estimations by the *Nagel* method show large intraindividual variation; there is considerable imprecision in the estimates, and the ability of the method to reach target ranges is poor when the clearance of caffeine is low (Tables 4 and 5).

In conclusion, the use of Bayesian forecasting methods to estimate caffeine clearance has been shown to be superior to the *Jost* and*Nagel* methods from a number of different perspectives, including accuracy, correlation to the *Gold Standard* method, intrasubject variation, and practical implementation. Metabolic liver function tests, such as the measurement of caffeine clearance, can be used as a research tool to assess hepatic function in a variety of liver diseases and possibly used for clinical purposes such as the prediction of the optimal time for transplantation and early detection of rejection in the posttransplant period. The *Jost* and *Nagel* methods should not be used for research purposes, particularly in subjects such as patients with liver disease who have low clearance of caffeine because there are more accurate techniques for the estimation of caffeine clearance. If serial measurements of caffeine clearance are to be contemplated for clinical purposes, then a simplified method with the best correlation to formal caffeine clearance measurements and a method with the least intrasubject variation should be used (i.e., in this study a method using Bayesian techniques). However, before the Bayesian methodology is used as a clinical test in observing liver function in patients with cirrhosis, further work using a greater number of serial measurements should be carried out to confirm the low intraindividual variation. In addition, its use in sick Child's C patients must be validated with formal measurement of caffeine clearance.

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Key Words: Caffeine; Clearance; Metabolism; Bayesian

IMAGE GALLERY

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Method	Healthy subjects (l/kg · hr)	Subjects with cirrhosis (l/hr · kg)
*Gold Standard**	0.116	0.039
Jost	0.106	0.021†
Nagel	0.131	0.047†
Least squares	0.117	0.039
Bayesian 2 conc. CV = 45%	0.115	0.038
Bayesian 2 conc. CV = 90%	ND	0.040
Bayesian 1 conc. CV = 90%	0.110	0.036
Bayesian 1 conc. CV = 90%	0.109	0.037

All results expressed as medians. ND, not done.
Healthy subjects, median of 32 estimations of caffeine clearance.
Subjects with cirrhosis, median of 19 estimations of caffeine clearance.
2 conc., Bayesian method using two caffeine concentrations to estimate clearance.
1 conc., Bayesian method using one caffeine concentration to estimate clearance.
CV = 90%, coefficient of variation for the population clearance value is doubled—see Methods Section.
* Clearance measure using intravenous infusion of labeled caffeine.
† Significantly different from *Gold Standard* method, $p < 0.05$.

Table 1

Method	Healthy subjects (r^2)	Subjects with cirrhosis (r^2)
Gold Standard*	—	—
Jost	0.70	0.93
Nagel	0.94	0.87
Least squares	0.94	0.99
Bayesian 2 conc. CV = 45%	0.91	0.22
Bayesian 2 conc. CV = 90%	ND	0.99
Bayesian 1 conc. CV = 45%	0.84	0.19
Bayesian 1 conc. CV = 90%	0.84	0.99

All results expressed as medians.
ND, not done; r^2, coefficient of determination; 2 conc., Bayesian method using two caffeine concentrations to estimate clearance; 1 conc., Bayesian method using one caffeine concentration to estimate clearance. CV = 90%, coefficient of variation for the population clearance value is doubled—see Methods Section.
* Clearance method using intravenous infusion of labeled caffeine.

Table 2

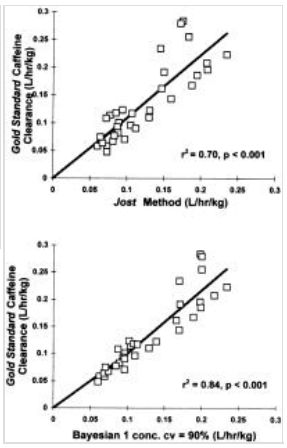

Fig. 1

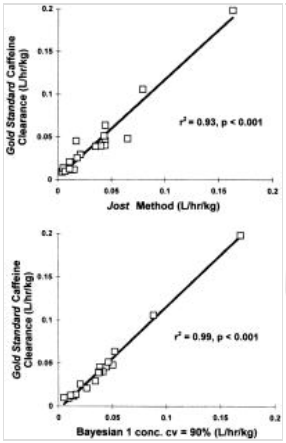

Fig. 2

Method	Healthy subjects	Subjects with cirrhosis
Jost	0.00245	−0.00519*
Nagel	0.00992†	0.00992†
Least squares	−0.00112	−0.00095
Bayesian 2 conc. CV = 45%	0.00185	−0.00025
Bayesian 2 conc. CV = 90%	ND	−0.00093
Bayesian 1 conc. CV = 45%	0.00042	−0.00025
Bayesian 1 conc. CV = 90%	0.00406	−0.00169

All results expressed as medians.
ND, not done; Healthy subjects, median error of 32 estimations of caffeine clearance; Subjects with cirrhosis, median error of 19 estimations of caffeine clearance.
* Significantly higher than all Bayesian 2 conc. median errors, $p < 0.05$.
† Significantly higher than *Jost* median error, $p < 0.05$.
‡ Significantly higher than all other methods, $p < 0.05$.
For all other abbreviations, see Table 1.

Table 3

Method	Healthy subjects	Subjects with cirrhosis
Jost	0.00022*	0.000061
Nagel	0.00016	0.000121
Least squares	0.00011	0.00001
Bayesian 2 conc. CV = 45%	0.00004	0.00001
Bayesian 2 conc. CV = 90%	ND	0.00000
Bayesian 1 conc. CV = 45%	0.00009	0.00001
Bayesian 1 conc. CV = 90%	0.00011	0.00001

All results expressed as medians.
ND, not done; Healthy subjects, median square error of 32 estimations of caffeine clearance; Subjects with cirrhosis, median square error of 19 estimations of caffeine clearance.
* Significantly higher than Bayesian 2 conc. and least squares median square errors, $p < 0.05$.
† Significantly higher than Bayesian 2 and 1 conc. (CV = 90%) median square errors, $p < 0.05$.
‡ Significantly higher than all other methods (except for *Jost*), $p < 0.05$.
For all other abbreviations, see Table 1.

Table 4

Target range	Jost (%)	Nagel (%)	LS (%)	B2 (%)	B2-CV (%)	B1 (%)	B1-CV (%)
Healthy subjects (within 10% of *Gold Standard*)	41	53	66	56	ND	44	53
Healthy subjects (within 20% of *Gold Standard*)	56	78	88	94	ND	78	81
Subjects with cirrhosis (within 10% of *Gold Standard*)	26	18	53	42	63	32	47
Subjects with cirrhosis (within 20% of *Gold Standard*)	42	35	68	74	74	58	84

ND, not done; LS, Least squares method; B2, Bayesian 2 concentration method; B2-CV, Bayesian 2 concentration (CV = 90%) method; B1, Bayesian 1 concentration method; B1-CV, Bayesian 1 concentration (CV = 90%) method.

Table 5

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