Backtracking booze with Bayes—the retrospective interpretation of blood alcohol data

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- 1 A Bayesian method is described which allows the explicit estimation of errors produced in estimating drug concentrations at times for which samples are not available for analysis.
- 2 This method was applied to the problem of 'backtracking' alcohol concentrations for medico-legal purposes.
- 3 Computer simulation allowed the effect of continuing alcohol absorption on the position and range of estimates of alcohol concentrations to be studied.

Keywords alcohol kinetics Bayes' theorem backtracking medico-legal aspects

Introduction

Interest in the forensic application of pharmacokinetic models was stimulated by the case of two motorists described in Gumbley *vs* Cunningham (1987). Their conviction was based on the back-calculation of blood alcohol concentration from the times of sampling to the times of the incidents under investigation.

In the first of these cases two brothers spent 2.25 h drinking in a public house before driving towards home across Birmingham. About 30 min later their car hit the wall of an underpass at high speed. The accident involved no other vehicle and there was no evidence of braking prior to the crash. Unfortunately, one of the brothers, the passenger, was killed. The driver refused to be breathalysed and was taken to a police station. Before a sample of blood could be taken for analysis he complained of feeling ill and was taken to the local hospital. Because of this there was a delay of 4 h 20 min between the incident and the time that a sample of blood was obtained. This sample was found to contain alcohol at a concentration of 59 mg % and on the basis of a rate of elimination of 10–25 mg % h⁻¹ the alcohol concentration at the time of the accident was estimated by backtracking calculation to be 120–130 mg %. The use of this method to estimate the blood alcohol concentration at the time of the accident was accepted by the magistrate, a ruling later confirmed by a judge at appeal. This decision has prompted several papers in the scientific and medical literature arguing strongly against the use of the backtracking technique (Dyer, 1988; Lewis, 1987; Taberner, 1988). Nevertheless, the calculation continues to be used in British legal practice. Although the cited authors stressed the theoretical possibility of errors in the estimates produced by the backtracking calculation, little attention was paid to the explicit estimation of such errors.

Questions raised by this use of pharmacokinetic modelling are as follows:

- 1) How does variability within the population of those parameters determining the elimination of ethanol translate into variability in the estimate of the blood ethanol concentration at the time of the incident?
- 2) Could ethanol consumed before leaving the public house but not yet absorbed bias the result, and would the time interval between drinking and the incident ensure that all the ethanol had been absorbed?
- 3) Could factors such as the amount of ethanol consumed or food taken with the ethanol alter the outcome?
- 4) How dependent are the results of backtracking calculations on the shape and position of distributions of population parameters?
- 5) Does the apparent non-linearity of ethanol disposition have to be considered?

We have applied a Bayesian method to illustrate the uncertainties involved in 'backtracking' blood ethanol concentrations in order to answer these questions. Bayes' theorem has previously been used in conjunction with sparse plasma drug concentration-time data and estimates of the population distributions of pertinent pharmacokinetic parameters to adjust drug dosage in individual patients (Whiting *et al.*, 1986). In these applications the precise shape of the posterior density, that is, the distribution of the likelihoods of producing the desired response for each of a range of doses, has been of relatively little concern. Only the dose with the highest likelihood is required and an algorithm introduced by Sheiner (1979) to determine the mode of this density has been used. However, when using this approach for medico-legal purposes both the shape and location of the posterior densities are of major importance. The

Bayesian method which we describe here has the advantage of estimating not only the mode of the density but also the likelihood of the full range of blood ethanol concentrations. Computer simulations incorporating the Bayesian algorithm have been used to demonstrate the effect of continuing ethanol absorption and non-linear elimination. The traditional methods of performing the backtracking calculation usually ignore these factors.

Part of this work was presented at the British Pharmacological Society meeting in Dublin, 1988 (Jackson *et al.*, 1988).

Methods

Application of Bayes' theorem

The formulation of Bayes' theorem for continuously distributed variables is given by equation 1 (Naylor & Smith, 1982). However, its application requires a multi-dimensional integration step which is difficult.

$$p(\theta; x) = \frac{l(x; \theta) \cdot p\theta}{\int l(x; \theta) \cdot p\theta \cdot d\theta} \quad (1)$$

where:

θ is a vector of parameter values.

x is the vector of data values.

$l(x; \theta)$ is the likelihood of the data calculated from the model for a given set of parameter values.

$p\theta$ is the joint probability of a given set of parameter values calculated from their individual prior distributions.

Until recently this has limited the use of Bayesian estimation where the parameters of the model are continuous variables. However, novel methods of integration (Smith *et al.*, 1985) may help to overcome this difficulty.

In preliminary studies we used a standard multi-dimensional Gaussian integrator (NAG algorithm D01FCF; van Dooren & de Ridder, 1976), but this was found to be unreliable for certain prior distributions of the parameters. Monte Carlo integration with importance sampling (Hammersley & Handscombe, 1964) was found to give reliable results for a wider range of prior distributions at the cost of increased computing time.

Equation 1 states the probability of a single set of parameter values, given the experimental data and the prior distributions of the parameters. What are required in the case of backtracking are the probabilities associated with each of a wide range of values of one of the parameters, e.g. the blood ethanol concentration at the time of the incident. This is termed the posterior marginal density, and for its estimation variability in parameters other than that of interest must be taken into account by a further integration over the full range of these parameters. The estimation of the chances of being above or below some arbitrary blood ethanol concentration is easily made on the basis of the ratio of areas under the posterior marginal distribution on either side of that limit.

Backtracking of blood ethanol concentrations

For the purposes of this work the example of backtracking ethanol concentrations was used, although the Bayesian method is equally applicable to other areas of forensic pharmacokinetics. Not only may forward or backward extrapolation be performed for the estimation of concentrations at times other than that for which data are available, but the question may be formulated so as to determine the time at which a known dose was ingested or administered. The principle of backtracking blood ethanol concentrations is illustrated in Figure 1. The subject consumes an unknown amount of ethanol during an undefined period of time. At some time $t(a)$, either during or after ethanol consumption, an incident occurs.

Figure 1 The basis of the backtracking calculation. Prior to time $t(o)$ an unknown amount of ethanol is consumed over a poorly defined time period. Following some delay an incident occurs at time $t(a)$ and later still a blood sample is taken at time $t(s)$. Back-extrapolation of the measured ethanol concentration allows estimation of the concentration at time $t(a)$.

Because of delays the sample of either blood, urine or breath for the measurement of the ethanol concentration is not taken at that time but at a later time, $t(s)$. The ethanol concentration at $t(s)$ may be below the prescribed legal limit, but by using a population average rate of elimination the concentration at the time of the incident may be estimated. Alternatively, the subject may have taken a dose of ethanol following the incident but before a sample was obtained for analysis. He or she then claims that a concentration above the limit is the result of this dose—the so called ‘hip flask’ defence. In this case, the backtracking calculation estimates the blood ethanol concentration at a given time using population values for the volume of distribution of ethanol as well as that of its clearance rate. Absorption is generally assumed to be complete.

The pharmacokinetic model

A simple pharmacokinetic model (Figure 2) assuming first order absorption from the gut and zero order elimination was used to describe the fate of ethanol after an oral dose taken prior to the time of an incident, $t(a)$. Zero order elimination was assumed as the K_m for ethanol elimination is generally much lower than the present legal blood ethanol limit (80 mg %), and deviations from a constant rate of elimination would be small (Forrest, 1986). At the time that drinking ceased an amount of ethanol $Aa(0)$ was assumed to be awaiting absorption in the gut. The blood ethanol concentration at the time of the incident is given as $C(a)$. Assay variability was included as a source of error with a constant coefficient of variation of 1% (Christmore *et al.*, 1984).

Parameter values

The times between cessation of drinking and $t(a)$ and between $t(a)$ and $t(s)$, as well as the blood ethanol concentration at $t(s)$, were taken from one of the original test cases (Gumbley *vs* Cunningham, 1987). For prior distributions of the rates of ethanol absorption and

elimination and of its volume of distribution the mean and variance of population values were taken from Holford (1987). Unfortunately, many of these data are old and there is a wide variation in estimates from the various sources.

The simple case

The simplest model studied was one in which it was assumed that further absorption did not take place following the incident. This mimicked the type of calculation used routinely for backtracking. The prior distributions for concentration of ethanol in the blood and the population distributions of elimination rate and volume of distribution are shown in Table 1. The time delay between the incident and the time the sample was taken for the estimation of the blood ethanol concentration ($t(a) - t(s) = 4 \text{ h } 20 \text{ min}$) was taken from Gumbley *vs* Cunningham (1987). The blood ethanol concentration at the time of sampling was 59 mg %. A uniform prior distribution was assumed for the blood ethanol concentration at the time of the incident in the range 0–200 mg %. This is equivalent to having very little knowledge about the blood ethanol concentration other than it was not a negative value.

The effect of continuing ethanol absorption on backtracking

Ethanol absorption will not cease immediately when drinking stops. Although absorption may be rapid it is controlled to a large extent by gastric emptying, and when this is delayed absorption can continue for some time after the final drink. To study the effect of this continued absorption, first order absorption of the ethanol remaining in the gut (Figure 1) was included in the model. Initially, the time lag between drinking and the incident was ignored.

The effect of dose

The effect of continuing ethanol absorption will depend upon the amount remaining in the stomach at the time when the subject takes his or her last drink. The size of this dose remaining in the gut at $t(o)$ was taken as unknown but limited maximally by the physical capacity of the stomach (McMinn & Hobdell, 1974) and the typical ethanol content of spirits (Martindale, 1989) (Table 1). To determine the effect of different doses of ethanol we have used three rectangular distributions (Table 1) to represent the range in which this amount of ethanol would be expected to lie. This form of distribution implies no prior knowledge about the dose apart from its maximum and minimum. In terms of drinks consumed the size of the three prior distributions studied for dose were 0–0.5, 0–5 and 0–50 units of ethanol, assuming a 10 g unit.

The effect of delay between drinking and crashing

Generally incidents do not occur immediately following drinking but after a delay. This commonly gives rise to the assumption that ethanol absorption is complete by

Figure 2 A pharmacokinetic model describing the absorption and elimination of ethanol. Absorption takes place according to a first-order process into a single body compartment. Elimination occurs by a single zero order process.

Table 1 Shape and distribution of model parameters

Figure	Aa(0) (g)		C(a) (mg %)		ko (mg l ⁻¹ min ⁻¹)		V(l)		ka	
	Shape	Range	Shape	Range	Shape	Range	Shape	Range	Shape	Range
3	—	—	R	0-200	N	3.3 ± 0.8	N	37 ± 3.7	—	—
4a	R	0-5	R	0-200	N	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
b	R	0-50	R	0-200	N	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
c	R	0-500	R	0-200	N	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
5a	R	0-50	R	0-200	N	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
b	R	0-500	R	0-200	N	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
6a	R	0-50	R	0-200	N	3.3 ± 0.8	N	37 ± 3.7	N	0.015 ± 0.004
b	R	0-500	R	0-200	N	3.3 ± 0.8	N	37 ± 3.7	N	0.015 ± 0.004
7a	R	0-50	R	0-200	LN	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
b	R	0-500	R	0-200	LN	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
8a	R	0-50	R	0-200	N	3.3 ± 0.8	LN	37 ± 3.7	N	0.15 ± 0.04
b	R	0-500	R	0-200	N	3.3 ± 0.8	LN	37 ± 3.7	N	0.15 ± 0.04
9a	N	2.5 ± 0.6	R	0-200	N	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
b	N	25 ± 6.0	R	0-200	N	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
10a	R	0-50	N	100 ± 25	N	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
b	R	0-500	N	100 ± 25	N	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
11a	R	0-50	R	0-200	N*	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04
b	R	0-500	R	0-200	N†	3.3 ± 0.8	N	37 ± 3.7	N	0.15 ± 0.04

R = rectangular; N = normal; LN = log-normal.

For non-rectangular $\mu \pm \text{s.d.}$ * $K_m = 7 \times 10^{-10} \pm 1.4 \times 10^{-10} \text{ mg l}^{-1}$; † $K_m = 70 \pm 17.5 \text{ mg l}^{-1}$.

the time of an incident. Such a delay may not only reduce the dose awaiting absorption but also increase the concentration of ethanol in the blood at the time of the incident. Thus the effect of delay can be complex and its magnitude may depend critically upon the rate of ethanol absorption. Estimating this rate of ethanol absorption is extremely difficult (Holford, 1987), and many of the estimates may be contaminated by the finite time taken to consume the ethanol. In addition, ethanol may slow its own absorption by delaying gastric emptying (Wilkinson *et al.*, 1977). External factors such as exercise (Volans, 1974) or pain (Nimmo, 1976) may also delay gastric emptying and hence the rate of ethanol absorption. Several authors (Sedman *et al.*, 1976; Taberner, 1988) have noted an effect of food upon the absorption of ethanol, both in its rate and extent. Because of these considerations the sensitivity of the shapes and positions of the posterior densities to changes in the rate constant of absorption have been studied by varying the rate of absorption in the model by a factor of 10.

The effect of changing the shape of the prior distributions

The Bayesian paradigm itself has relatively few assumptions, mostly relating to the model. However, assumptions have to be made about the form and position of the prior distributions and some of these are based on minimal information. Often the distribution of population parameters is estimated by a method which necessitates an *a priori* assumption about the form of this distribution (Beal & Sheiner, 1980). Non-parametric methods (Mallet, 1986) which do not impose a distributional form have been developed but are not in widespread use. It is, therefore, important to study the effect on the outcome of variations in these assumptions. To

do this we have studied the effect of varying the shape of the prior distributions. Thus, separate simulations were performed under the assumption that the population distribution of ethanol clearance rates was either normal or log normal. To produce a log normal distribution with a similar mean and variance to that of the normal distribution the delta method was used (Lindgren, 1968). A similar modification was made for the estimates of the volume of distribution, replacing the normal prior with a log-normal distribution but retaining the same mean and variance.

Our initial assumption about the dose of ethanol consumed was that we had no prior knowledge of its amount. However the investigator may have a crude estimate of dose but would still like to accommodate the possibility of much higher or lower doses. To achieve this a non-uniform prior distribution such as a Gaussian can be used with its mean at the most likely dose and its tails representing the lower probability of higher and lower doses. One of the features of Bayesian estimation that concerns some workers is that the outcome may be dependent upon this choice of prior distribution. For ethanol backtracking the most obvious prior distribution which could affect the posterior density is that of the blood ethanol concentration at the time of the incident. To determine the effect of changing the shape of this distribution we have replaced the rectangular distribution, which suggested total ignorance of the likely concentration, with a Gaussian distribution which suggests some prior knowledge.

The effect of non-linear elimination on backtracking

The basic pharmacokinetic model is simplistic in that the elimination of ethanol is assumed to be zero order at all

blood ethanol concentrations (Lewis, 1986). In an attempt to overcome this we investigated an alternative model where the rate of elimination was described by the Michaelis Menten equation. Thus, the differential equations describing both absorption and elimination had to be integrated numerically using a Bulirsch-Stoer method (Press *et al.*, 1986), although the cost in computer time was very high (170 h on a 20 Mhz 80386 based PC + 80387). Two simulations were performed, the first with a very low value of K_m ($7.0 \times 10^{-10} \text{ g l}^{-1}$), in order to reproduce linear elimination as a check of the algorithm, and the second with a K_m value of 70 mg l^{-1} estimated from population data (Rangno *et al.*, 1981).

Results

In the simple case without continuing absorption the variability in the predicted blood ethanol concentration at the time of the incident was low (Figure 3). The proportion of the area below 80 mg % was small and, therefore, the likelihood of making a conviction in error is small. However, when the model was extended to include ethanol absorption which continues after the cessation of drinking the possibility of the blood ethanol concentration at time $t(a)$ being below the legal limit ceased to be negligible (Figure 4). When large (Figure 4b) or very large (Figure 4c) quantities of ethanol have been consumed then the proportion of the area under the posterior distribution curve below 80 mg % is still greater (Table 2). As illustrated in Figure 5a, b this effect diminishes when the time between cessation of drinking and $t(a)$ increases to 30 min, the delay in the Gumbley case. These results should be compared with those shown in Figure 4b, c using the equivalent ethanol doses. The effect of increasing the time between drinking and $t(a)$ depends upon the rate at which the ethanol is absorbed. When the same doses as those used to construct Figure 5 were used but with a 10 fold lower rate of absorption the proportion of the curve below 80 mg % increased for both doses (Figure 6a, b).

Figure 3 The posterior distribution (probability of each value of the range of ethanol concentrations considered) of blood ethanol concentration at the time of the incident, $t(a)$, assuming that absorption does not continue beyond the time drinking stops. For this and subsequent Figures the delay between the incident and sampling, $t(a)-t(s)$, was 4 h 20 min and the blood ethanol concentration at the time of sampling was 59 mg %.

To generate the data for Figures 7 and 8 the prior distributions of the population clearance and volume of distribution values were transformed to be log normal in shape yet retaining the initial means and variances. These results should, therefore, be compared with those for the same doses shown in Figure 4. Although the shapes of the posterior densities were altered the change was small and the proportion of the area below 80 mg % changed hardly at all (Table 2). Thus, the method was shown to be robust to variations in the assumptions about the population distribution of parameters. In Figure 9a, b we show the results when the original rectangular shape for the prior distribution of the dose of ethanol was replaced by a normal distribution with a mean at the mid-point of the rectangular distribution and a standard deviation of one quarter of the mean. These panels should be compared with Figure 4a, b. The same argument was applied to the distribution of ethanol

Figure 4 The posterior distribution of blood ethanol concentration at the time of the incident assuming that absorption continues after drinking ceases. Ethanol remaining in the gut when drinking ceases: a) 5g, b) 50 g, c) 500 g.

Figure 5 The posterior distribution of blood ethanol concentration at the time of the incident assuming absorption continues following drinking with a delay of 30 min between stopping drinking and the time of the incident. Ethanol remaining in the gut when drinking ceases: a) 50 g, b) 500 g.

Figure 6 The posterior distribution of blood ethanol concentration at the time of the incident assuming absorption continues following drinking with a delay of 30 min between stopping drinking and the time of the incident but with a reduced absorption rate constant k_a of 0.015. Ethanol remaining in the gut when drinking ceases: a) 50 g, b) 500 g.

Figure 7 The posterior distribution of blood ethanol concentration at the time of the incident assuming absorption continues following drinking. The rate of elimination of the ethanol is log-normally distributed within the population. Ethanol remaining in the gut when drinking ceases: a) 50 g, b) 500 g.

Figure 8 The posterior distribution of blood ethanol concentration at the time of the incident assuming absorption continues following drinking. The volume of distribution of ethanol is log-normally distributed within the population. Ethanol remaining in the gut when drinking ceases: a) 50 g, b) 500 g.

Table 2 The percentage of area under each posterior density below 80 mg %

Condition	Dose Aa(0) (g)	Percentage < 80 mg %
No absorption	—	0.2
Absorption no delay	5	0.5
	50	52.8
	500	56.6
Absorption + delay	50	0.3
	500	6.0
Absorption (slow) + delay	50	4.1
	500	56.1
Absorption no delay LN CL	50	53.1
	500	57.2
Absorption no delay LN V	50	52.8
	500	56.9
Absorption no delay N C(a)	50	52.9
	500	56.8
Absorption no delay low K_m	50	52.9
Absorption no delay norm K_m	50	56.2

N = normal; LN = log normal; CL = clearance; V = volume of distribution; C(a) = concentration at time of incident; Aa(0) = amount in gut when drinking ceases.

Figure 9 The posterior distribution of blood ethanol concentration at the time of the incident assuming absorption continues following drinking. The prior hypothesis relating to the dose of ethanol in the gut is that it has a normal distribution. Ethanol remaining in the gut when drinking ceases: a) mean 2.5 g, b) 25 g.

concentration in the blood at the time of the incident. Thus, the effect of replacing a rectangular distribution with a normal distribution of mean 100 mg % and standard deviation 25 mg % is illustrated by comparing Figure 10a, b with Figure 4b, c.

The algorithm used for integration was shown to be adequate since, when the K_m was kept low, the posterior density (Figure 11a) was indistinguishable from that of the linear model with the same starting dose (Figure 4a). Using the experimentally determined value of K_m there was only a slight change in the position of the posterior density (Figure 11b). This is perhaps not surprising as the end concentration studied was well above the range where non zero-order kinetics become apparent.

Discussion

Ethanol consumption is a major cause of road traffic accidents (Haberman & Baden, 1978) and measures to discourage drinking and driving are appropriate. However, care is necessary when pharmacokinetic calculations are applied to estimate ethanol concentrations for times other than those at which the blood ethanol is actually measured. The method needs to account for possible variations from several sources. The simplest are those arising from the assay. However, these are well documented and generally small in magnitude. A further source of error will arise as a result of approximations to physiological reality imposed by the use of a simple pharmacokinetic model. The major possible source of error is seen when continuing absorption is ignored, as this can make a large difference to the shape and position of the posterior density. To a limited extent we have allowed for deviation from zero-order elimination, showing that the results are relatively insensitive to this phenomenon. In addition, altering the assumed population parameter distributions was found to have little

Figure 10 The posterior distribution of blood ethanol concentration at the time of the incident assuming absorption continues following drinking. The prior hypothesis relating to the blood concentration of ethanol at the time when drinking stops is that it has a normal distribution. Ethanol remaining in the gut when drinking ceases: a) 50 g, b) 500 g.

Figure 11 The posterior distribution of blood ethanol concentration at the time of the incident assuming absorption continues following drinking and that the elimination of ethanol from the blood follows a non-linear Michaelis-Menten mechanism. K_m value: a) $7 \times 10^{-10} \text{ mg l}^{-1}$, b) 70 mg l^{-1} . Ethanol remaining in the gut when drinking ceases: 5 g.

effect on the final likelihood distribution. The prior hypothesis required for the parameter under investigation (here the blood alcohol concentration) is found to have little influence upon the posterior distribution (Figure 10a, b). A final source of error arises from the unique status of the observed subject. Thus, there is generally no information as to his or her position in the population distribution of the parameters describing ethanol elimination. When such parameters are related strongly to demographic factors such as age (Vestal *et al.*, 1977), sex (Holtzman *et al.*, 1985), race (Bennion & Li, 1976) or previous drug exposure (Jones & Jones, 1984), they may be modified to describe the subject

more closely. However, there will always be a range within which the subject's unique values will lie. Our results show that in the absence of continuing absorption, reasonably robust estimates of blood ethanol concentrations at preceding times can be made. However, when absorption continues after drinking, especially when at a slow rate, backtracking calculations may become markedly inaccurate.

Computer Hardware for this study was supported by donations from the University of Sheffield Research Fund and the Hallamshire Therapeutics Research Trust.

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(Received 22 March 1990,
accepted 7 September 1990)