Blood alcohol concentration and psychomotor effects

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This study assessed the effect of intravenous alcohol infusions on psychomotor impairment and compared it with that of alcohol administered orally. Comparisons were made between three European drink-driving limits of blood alcohol concentration (BAC) (20, 50 and 80 mg 100 ml^{-1}) and an oral dose of alcohol 0.75 mg kg^{-1}. Twelve volunteers, aged 22–34 yr, were recruited. At targets of 20, 50 and and 80 mg 100 ml^{-1}, the mean (SD) BAC was 22.1 (3.7), 51.5 (3.3) and 80.5 (4.2) mg 100 ml^{-1}, respectively. The peak BAC following an oral dose of alcohol 0.75 mg kg^{-1} ranged from 19 to 68 mg 100 ml^{-1}. In psychomotor testing, choice reaction time deteriorated with increasing BAC and showed significant differences between baseline and the 50 ($P<0.05$) and 80 mg 100 ml^{-1} ($P<0.01$) conditions. Dual-task secondary reaction time deteriorated with increasing BAC and showed a statistically significant difference between all groups and baseline (oral and 20 mg groups, $P<0.05$; 50 and 80 mg groups, $P<0.01$). Dual-task tracking in the 50 and 80 mg groups was significantly different from baseline ($P<0.05$ and $P<0.01$, respectively). Oral dosing resulted in widely variable BACs, making it difficult to assess psychomotor impairment reliably. An intravenous infusion enables the BAC to be maintained within a narrow range. This allows precision when investigating the effects of alcohol on psychomotor performance.

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Post-operative psychomotor performance is commonly assessed in anaesthetic research when studying recovery from general anaesthesia, and includes assessment of fitness to drive. One of the difficulties encountered when making such assessments is the fact there is no standard against which to compare evidence of performance impairment. It is, therefore, difficult to define the minimally acceptable degree of postoperative impairment and to determine how soon it is safe to drive after a general anaesthetic for a day surgery procedure.

The World Health Organization previously recommended that the behavioural effects of drugs be compared with those of alcohol.[1] The logic of such an approach is that degrees of performance impairment have been established for levels of various blood alcohol concentration (BAC) with subsequent implications for supposed 'fitness to drive'. Thus, where recovery from an anaesthetic drug is associated with performance impairment similar to, or greater than, that seen with a given BAC, there may be grounds for concluding that the impairment would have real-life consequences. Governments, however, vary in legislation regarding permitted BACs when driving, with the result that there are different legal 'limits' around the European Union: for example, BACs of 20, 50 and 80 mg 100 ml^{-1} in Sweden, France and the UK, respectively. These values were used in the present study as the target points at which psychomotor impairment would be assessed.

The effects of blood alcohol on tasks that simulate driving skills have been studied widely.[2–4] Typically, the method involves administering an oral dose of alcohol and then assessing the behavioural changes produced. Oral doses of alcohol can, however, produce considerable variability in pharmacokinetic variables such as the peak BAC, the time to achieve peak concentration and the time course of decay in blood concentration, because of differing bioavailability.[5–7] Moreover, as psychometric assessment of alcohol-

induced impairment is conducted in a dynamic situation where the alcohol concentration is increasing or decreasing, it can be difficult to compare results of assessments which follow one another.

The present study was designed to assess psychomotor impairment during intravenous administration of alcohol compared with oral dosing. We administered alcohol first by the conventional single oral dose and then by the intravenous route to maintain a steady BAC. The effects of BAC on the skills required in driving were assessed by two psychomotor tests.

Methods

Subjects

Following local ethics committee approval, 12 healthy volunteers (nine male, three female; mean (range) age 30 (22–34) yr; mean (range) weight 76.5 (58–86.5) kg) participated in the study after giving informed written consent. Their history of alcohol use was moderate (range 3–35 units per week). A full medical history was taken and any volunteer with a history of cardiac, pulmonary, neurological, hepatic or renal disease, psychiatric disorder or substance misuse was excluded. Subjects were instructed not to eat or drink for 4 h before the study nor to drive a car or operate any heavy machinery the evening after the study. Subjects were informed that they would receive a volume of alcohol to drink, followed by an alcohol infusion, and that the maximum blood alcohol level would not exceed the maximum permitted BAC for driving in the UK. All subjects were driven home after the study.

Assessments took place in a laboratory in the Department of Anaesthesia and lasted approximately 5 h. The subject and at least one investigator were present for each session. On arrival, two intravenous cannulae were inserted, one in each arm. One cannula was used for blood sampling and the other for administering intravenous alcohol. The alcohol analyser (Lion Alcolmeter; Lion Laboratories Ltd, Barry, UK) was calibrated according to the manufacturer's instructions. Breath analysis of blood alcohol was used to confirm that the volunteers had abstained from alcohol as required. The 12 volunteers then repeatedly performed the psychomotor tests to reduce any discernible practice effect and to establish a set performance baseline. Subjects were unaware of the dose of alcohol consumed. All received an initial single oral dose of alcohol 0.75 g kg^{-1} (of 40% vodka) diluted up to a volume of 350 ml in fresh orange juice and consumed over 15 min. Breath analysis of BAC was then performed at 3 min intervals until a plateau was reached. This was recorded as the peak. This produced a large spread of peak BAC, from 19 to 68 mg 100 ml^{-1}. When the peak BAC had been achieved, the subject was asked to perform a set of psychometric tests. After completion of the psychomotor tests, breath analysis of BAC was performed every 3 min during the fall in BAC. When the BAC had decreased to approximately 20 mg 100 ml^{-1}, as measured by breath analysis, an intravenous infusion of alcohol (5% in 0.9% saline solution) was commenced.

The rate of infusion of alcohol was altered by the investigator in response to the measured BAC displayed on the breath analyser. The aim was to maintain the BAC steady at a concentration of 20 mg 100 ml^{-1}, then at 50 mg 100 ml^{-1} and finally at 80 mg 100 ml^{-1} for 30 min each. The BAC was analysed using the breath analyser as frequently as required (approximately every 3 min) until a steady-state BAC was achieved and then measured before and after each set of psychometric tests. Once a subject's BAC had reached a stable value of 50 mg 100 ml^{-1}, they were asked whether they would feel capable of driving a car safely if required to do so in the event of an emergency. During the experiments, the subjects had one or more blood samples taken to assess the correlation between the breath-assessed BAC measured by the Alcolmeter and the blood-assessed concentration measured using a liquid phase chromatographic technique. The subjects relaxed between psychometric assessments by reading or listening to the radio.

Psychomotor testing

Subjects repeated two psychomotor tests on a personal computer. Computerized tasks[8] of dual-task tracking and secondary reaction time and choice reaction time were chosen for their known sensitivity to the sedative effects of alcohol and other drugs.[9 10] The tests were performed before alcohol administration, then at the peak BAC after the oral dose, and then repeated three times each at 15 min intervals at 20, 50 and 80 mg 100 ml^{-1}. This gave a total of 11 sets of psychomotor test data for each subject including the baseline assessment.

Primary tracking and secondary visual reaction time

Subjects operated a computer mouse to control an on-screen icon (a cross) with the task of maintaining it in contact with a 'target' circle moving at varying velocity and direction across the screen of a visual display unit (VDU). The primary task score was the time spent 'on target' (i.e. the proportion of total time spent tracking during which the cross was kept in contact with the circle) expressed as the root mean square error (r.m.s.). While performing the tracking test, subjects had also to respond by pressing the keyboard spacebar when visual signals (star-shaped icons) appeared unpredictably at the edges of the VDU. Secondary task performance was recorded in milliseconds.[11]

Choice reaction time

Five numbered circles were displayed on the VDU, each corresponding spatially to response keys '1' to '5' on the adjoining keyboard. During each trial, the subject's dominant hand rested on the keyboard spacebar. After a variable

interval, one of the circles randomly changed colour, requiring the subject to remove their hand from the spacebar and press the appropriate response key. Reaction time was expressed in milliseconds as 'decision time' (time taken to lift the hand off the spacebar) and 'movement time' (move to the response key).[12]

Data were stored and analysed using Minitab software version 10. The prediction error and absolute prediction error were calculated to display the relationship between the predicted BAC as measured by breath analysis and the measured BAC.[13] An underestimate of the measured BAC by breath analysis was defined as a positive prediction error. An overestimate of the measured BAC by breath analysis was defined as a negative prediction error. Bias and precision were also calculated. A positive bias was defined as an underestimate of the measured BAC by breath analysis. Psychomotor performance was expressed as a mean change from baseline for each condition. The repeated-measures design was subjected to balanced analysis of variance. Significant main effects were investigated further by pairwise comparison of means using *t*-test, and Bonferroni correction as appropriate. All-alpha values were two-tailed and those <0.05 were considered to indicate statistical significance.

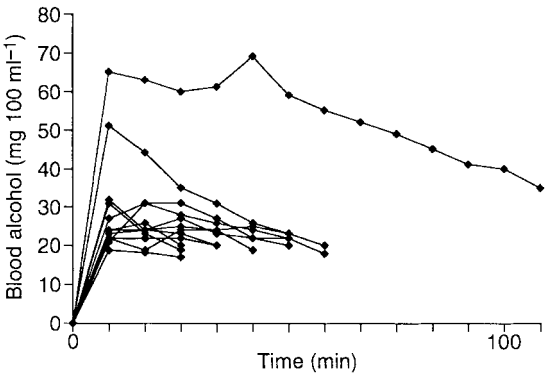

Fig 1 Variability of peak breath estimated blood alcohol concentration and subsequent decay in 12 volunteers after administration of a standard, oral dose (0.75 ml kg^{-1}).

Results

Blood alcohol concentration

Conventional single oral dose

Twenty minutes after oral consumption of alcohol, the mean (SD) peak breath alcohol concentration was 32 (14) mg 100 ml^{-1} with a range from 19 to 68 mg 100 ml^{-1}. The time for the oral dose to decay to an estimated BAC of 20 mg 100 ml^{-1} also showed marked variation, from 35 to >100 min (Figure 1).

Intravenous infusion technique

At the 20, 50 and 80 mg 100 ml^{-1} targets, the mean (SD) BAC was 22 (4), 52 (3) and 81 (4) mg 100 ml^{-1} (Figure 2).

There was a close correlation between the measured BAC and the breath-predicted values (r=0.84), but there was a general tendency for the breath to underestimate the blood concentration (Figure 3). The bias at 50 mg 100 ml^{-1} was 8.6% with a precision of 8.7%; at 80 mg 100 ml^{-1}, the bias was 22.8% with a precision of 22%. The individual subject precision error and the mean absolute prediction error increased progressively with greater BACs.

Psychomotor testing

Results of the choice reaction time task and the dual-task showed the expected wide variation between subjects (expression of performance as a change from baseline reduces such variation).[14] No significant differences were observed within subjects in choice reaction time or in primary tracking with secondary visual reaction during

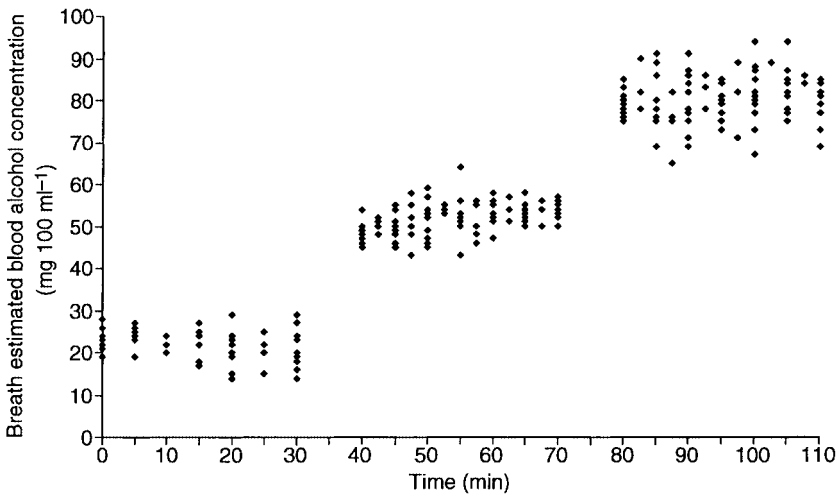

Fig 2 Variability of breath-estimated blood alcohol concentration in 12 volunteers after administration of continuous intravenous infusions to maintain target blood concentrations of 20, 50 and 80 mg 100 ml^{-1}.

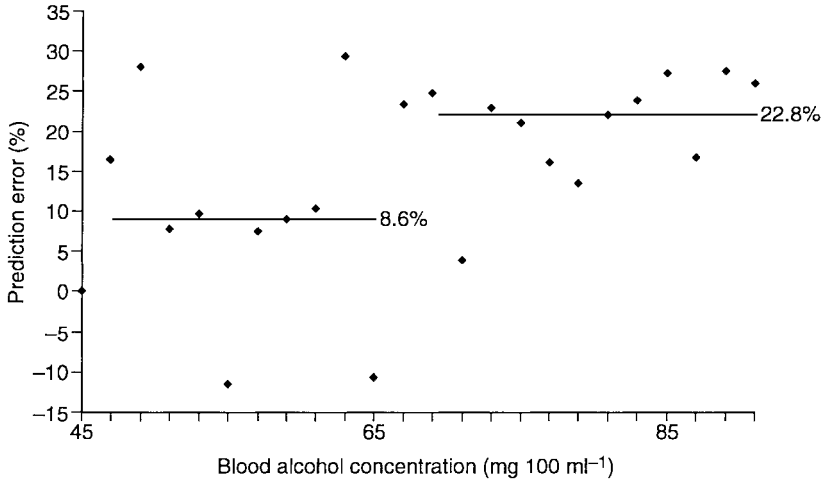

Fig 3 Prediction error of breath-estimated blood alcohol concentration (%) at various directly measured blood alcohol concentrations between 45 and 90 mg 100 ml^{-1}. An underestimate of blood alcohol concentration by the breath estimate is expressed as a positive prediction error. Mean prediction errors at 50 and 80 mg 100 ml^{-1} target concentrations are displayed as solid lines.

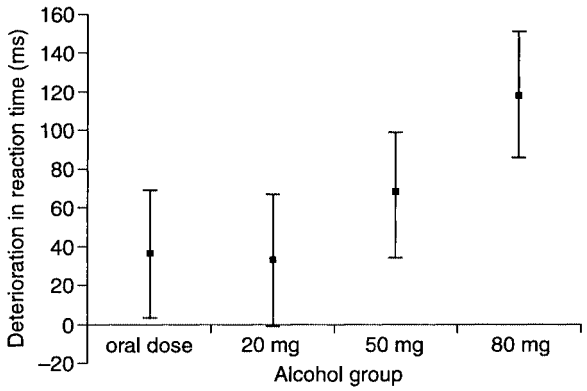

Fig 4 Deterioration in choice reaction time recorded in milliseconds in 12 volunteers with increasing blood alcohol concentration. Values are means (5–95% confidence interval). Alcohol groups: oral dose, maximum blood concentration following the oral dose; '20 mg', '50 mg' and '80 mg' are target concentrations of 20, 50 and 80 mg 100 ml^{-1}, respectively.

repeat testing over the 30 min periods when the BAC remained steady.

Choice reaction time

There was a significant increase ($P<0.01$) in choice reaction time as BAC increased (Figure 4). Further analysis confirmed that there was a significant difference between the 50 and 80 mg responses compared with baseline ($P<0.05$) (Table 1).

Dual-task performance

Secondary visual reaction time

As BAC increased, secondary reaction time performance deteriorated significantly ($P<0.01$; see Figure 5). There was a significant difference between all alcohol concentrations and baseline and between 20 mg and 50 and 80 mg ($P<0.05$) (Table 1).

Tracking

Tracking performance deteriorated significantly with increasing BAC ($P<0.01$; Figure 6). This deterioration was significant between the 50 and 80 mg alcohol conditions and baseline, and between the 20 and 80 mg conditions ($P<0.05$).

In the subjective assessment of fitness to drive at 50 mg 100 ml^{-1}, all subjects felt that their psychomotor performance was affected at this BAC and stated that they felt incapable of driving a car even in the event of an emergency.

Discussion

The use of alcohol as a comparator or benchmark for other drugs has been recommended by the World Health Organization,[1] and various studies have applied the concept,[15–18] but, with conventional oral administration, achieved a variety of BACs. Thus the matter of establishing any 'standard' criteria for impairment is complex. Nonetheless, Tiplady[19] has described the potential value of alcohol as a comparator to assess the effects of anaesthetic agents (although with several important caveats) in that its dose-related effects upon psychomotor performance are reasonably well established. There is also the virtue that BACs are set as (arbitrary) threshold standards for fitness/non-fitness to drive. It is, however, one thing to show equivalence in 'impairment' but another to establish whether the degree and nature of the impairment are of clinical or practical significance. Tiplady has noted that test performance 'cannot be validated in a strict sense against the likelihood of road accidents (or of accidents at home or at work, for that matter)' (ref. 19, p.33). We would agree that alcohol is a useful comparator and that the legal reference points of 20, 50 and 80 mg 100 ml^{-1} BAC have

Table 1 Deterioration in performance with choice reaction time (CRT), secondary reaction time (SRT) and tracking at different blood alcohol concentrations. *Significantly different from baseline and from blood alcohol concentration of 20 mg 100 ml^{-1} (P<0.01)

	CRT (ms^{-1})	SRT (ms^{-1})	Mean deterioration (95% CI) Tracking (%)
Oral dose	36 (3–69)*	31 (11–57)*	–1 (–3 to 1.0)
20 mg 100 ml^{-1}	33 (–1 to 67)	35 (16–56)*	–1.5 (–3.6 to 0.6)
80 mg 100 ml^{-1}	68 (34–99)*	86 (66–106)**	–3.2 (–5.2 to –1.13)*
100 mg 100 ml^{-1}	118 (86–151)**	120 (100–140)**	–7.8 (–9.8 to –5.8)**

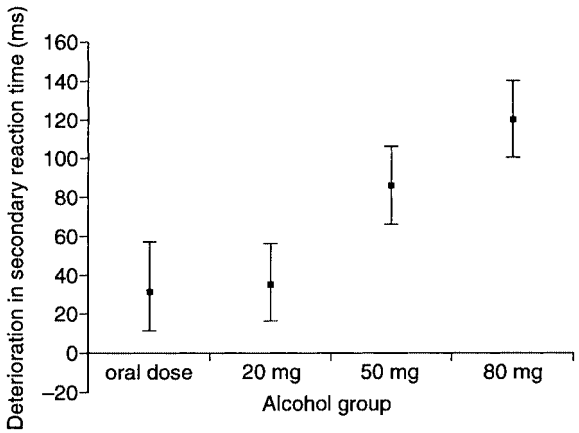

Fig 5 Deterioration in secondary reaction time recorded in milliseconds in 12 volunteers with increasing blood alcohol concentration. Values are mean (5–95% confidence interval). Key as in Figure 4.

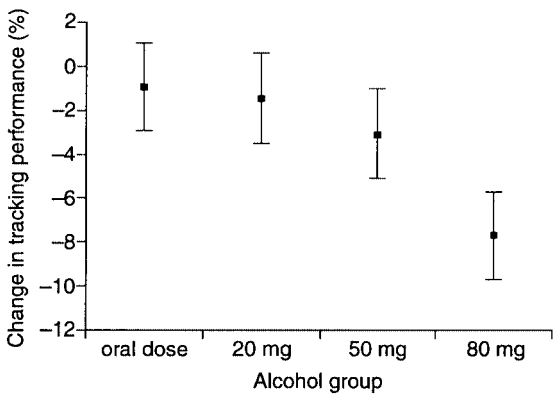

Fig 6 Deterioration in tracking performance recorded as a percentage of time on target in 12 volunteers with increasing blood alcohol concentration. Values are mean (5–95% confidence interval). Key as in Figure 4.

merit as standards against which recovery from anaesthesia or any other psychoactive drugs can be compared. This could help standardize further research and allow valid comparisons to be made between future studies.

In the present study, after oral dosing, there was considerable variability in the peak BAC achieved and in its rate of decay (Figure 1). This pharmacokinetic variability can be reduced using a continuous intravenous infusion. We demonstrated that it was possible to maintain a steady BAC for a prolonged period of time in an individual by using an intravenous infusion. Moreover, with continuous infusions, the concentration could be adjusted easily to the values required for a comparative investigation between different BACs. By maintaining BACs within narrow ranges, we demonstrated the effect of changes in BAC on psychomotor performance. The use of a breath Alcolmeter as a guide to adjust infusion rates allowed compensation for variations in individual pharmacokinetics and constant BACs to be achieved.

The difference between the breath-estimated and blood-measured BACs was greater at higher concentrations. A difference between breath-estimated BAC and blood sample BAC was also observed by Jones and Andersson.[20] The blood and breath alcohol estimates in their study were simultaneously taken from suspected 'drunk drivers' stopped for motor vehicle offences. These authors concluded that bias could be caused by a variety of factors, including the calculation used by manufacturers to correct for the blood:breath ratio, and metabolism of alcohol within the blood samples over time. The present study used a continuous infusion. This itself could result in a difference between breath and blood estimates. Davidson and co-workers[21] reported differences between estimated pharmacokinetic propofol concentrations and measured serum concentrations. This difference was decreased by temporarily stopping the infusion during the blood-sampling period. Davidson and colleagues concluded that the bias observed could be the result of constant addition to the vascular compartment by the propofol infusion. This could also hold true for the alcohol infusions used in this study.

The psychomotor tests employed in this study have previously been shown to be sensitive to the effects of psychoactive drugs such as sedatives, alcohol and anaesthetics.[22 23] Moreover, the present results replicate the impairment of performance by alcohol seen in previous studies,[9 24] including our recent work, with implications for real-life highly skilled performance.[25] The results confirm that oral administration and infusion of alcohol have similar effects on the results of the psychomotor tests. The validity of performance tests, particularly with respect to driving, has been discussed widely. While, as Tiplady has observed, the tests cannot be validated against the likelihood of road accidents, they do have content, criterion and face validity. Normative data for these tests are available with reference to previous published work.[8 25] The tasks have face validity in that they do reflect the requirements of real-life skills such as driving.[26]

Previous, important performance studies by Thapar and co-workers[15 17] and Liguori and colleagues[3] used oral doses

of alcohol; performance rose and fell with inevitable changes in BAC. Thapar and co-workers used only peak BAC as their steady-state reference point, hence providing a rather narrow window of observation and consequently a small number of data points. In addition, Thapar and colleagues achieved an average peak BAC of 110 mg 100 ml^{-1}. This BAC is substantially higher than that of any European drink-driving limit. Thapar and co-workers concede that the impairment detected at a BAC of 110 mg 100 ml^{-1} is probably too high to use as a valid comparator in assessing recovery from anaesthesia. During subjective assessment in the present study, subjects felt unable to drive safely at a BAC of only 50 mg 100 ml^{-1} and dual-task assessment of secondary reaction time revealed a statistically significant difference from baseline performance a BAC of only 20 mg 100 ml^{-1}.

The maximum performance impairment in the present study occurred at a target BAC of 80 mg 100 ml^{-1}. A mean increase of 120 ms^{-1} was found for both the choice and secondary reaction times at this BAC. If this result was translated into driving a vehicle, the increase in braking distance would be some 4 m while travelling at 70 m.p.h. (112 km h^{-1}). The volunteers' subjective assessment of their impairment was that they would be incapable of driving safely at a BAC of 50 mg 100 ml^{-1}, and this was confirmed by the objective psychomotor tests. Our results contribute to the increasing literature that supports the British Medical Association's recommendation that the UK permitted BAC for driving be reduced to 50 mg 100 ml^{-1}.

We believe that we have demonstrated that it is possible to achieve greater control of chosen BACs, and subsequently to measure more precisely the degree of performance impairment, by using the intravenous administration technique. This will allow investigators to compare with greater accuracy the impairment caused by alcohol and other drugs in future.

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