doi:10.1111/j.1360-0443.2007.01802.x

Age- and gender-related differences in blood amphetamine concentrations in apprehended drivers: lack of association with clinical evidence of impairment

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ABSTRACT

Background New legislation aimed at combating driving under the influence of drugs (DUID) in Sweden stipulated zero-concentrations in blood for scheduled substances. DUID suspects ($n = 300$), with amphetamine as the only psychoactive drug identified in blood, were investigated in relation to age and gender. In a smaller retrospective sample ($n = 70$) the relationship between clinical tests of impairment were compared with the concentration of amphetamine in blood. **Measurements** All forensic blood samples were subjected to a broad toxicological screening analysis by immunoassay methods [enzyme multiplied immunoassay technique/cloned enzyme donor immunoassay (EMIT/CEDIA)] and positive results were verified by gas chromatography-mass spectrometry (GC-MS). The limit of quantitation (LOQ) for determination of amphetamine in blood was 0.03 mg/l. People suspected of being under the influence of drugs were examined by a physician who asked various questions about state of health and use of drugs and also administered simple psychomotor and cognitive tests of impairment. After conducting these tests the physician concluded whether the suspects were not impaired, slightly, moderately or highly impaired by drugs other than alcohol. **Findings** Among 300 DUID suspects with amphetamine in blood there were 246 men (82%) and 54 women (18%). Mean age (± SD) of the men was 37.1 ± 8.7 years compared with 35.5 ± 7.1 years for the women ($P > 0.05$). The frequency distribution of blood amphetamine concentration was positively skewed with mean, median and highest values of 1.0 mg/l, 0.9 mg/l and 7.1 mg/l, respectively. The mean concentrations were slightly higher in the women 1.11 mg/l (median 1.0 mg/l) compared with 0.97 mg/l (median 0.8 mg/l) in the men ($P > 0.05$). There was a weak but statistically significant correlation between the person's age and the concentration of amphetamine in blood ($r = 0.18$, $P < 0.05$). The results of clinical tests of impairment showed no relationship with the concentration of amphetamine in blood according to analysis of variance ($P > 0.05$). **Conclusions** The lack of association between degree of drug influence and the concentration of amphetamine in blood speaks against the notion of introducing concentration *per se* limits or graded penalties depending on the blood-concentration of this stimulant. Zero-concentration limits or LOQ-limits are a much more pragmatic way to enforce DUID legislation.

Keywords Amphetamine, blood-concentration, DUID, impaired driving, zero-limits.

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Submitted 14 September 2006; initial review completed 22 December 2006; final version accepted 11 January 2007

INTRODUCTION

Since the introduction of zero concentration limits in blood for driving under the influence of scheduled drugs in Sweden (1 July 1999), the number of cases of driving under the influence of drugs (DUID) submitted by the police for toxicological analysis has increased more than 10-fold [1,2]. The vast majority of blood samples analysed (85%) contain one or more banned substance and illicit drugs dominate over prescription drugs [1–3]. Indeed, polydrug use is the norm in DUID suspects, which tends to complicate the relationship between the concentration of a specific drug and the effects on a person's performance and behaviour,

owing to various drug–drug and drug–alcohol interactions [3,4].

Amphetamine is the foremost drug of abuse in Sweden and this central stimulant has maintained this position over several decades [5,6]. Misuse of amphetamine and other stimulants accelerated in the 1960s, being used as pick-me-ups and slimming pills, as exemplified by the anorectic agent phenmetrazine or Preludin [5]. Amphetamine soon dominated as the drug of choice and higher doses and a switch to intravenous administration led to greater dependence liability [6]. Increasing the dose caused more intense feelings of wellbeing, gave extra energy and drive, a reduced appetite and less need for sleep [7,8]. Chronic administration of amphetamine leads to many undesirable effects such as psychotic episodes, emotional instability, paranoid delusions, anxiety and insomnia [6–8].

This paper reports the concentrations of amphetamine in blood samples from DUID suspects apprehended in Sweden when this central stimulant was the only psychoactive substance present. The concentrations of amphetamine were evaluated in relation to age and gender of the offenders. In a smaller retrospective sample the concentration of amphetamine in blood was compared with the results from clinical tests of impairment and a questionnaire to assess degree of drug influence.

MATERIALS AND METHODS

Selection of DUID suspects

All blood specimens from people suspected of driving under the influence of alcohol and/or drugs in Sweden are sent for toxicological analysis to one central laboratory (the National Laboratory of Forensic Chemistry, Linköping). The first suspicion of impairment arises when the driver is stopped and questioned by the police because of a moving traffic violation, a crash or when routine sobriety controls are made. If the result of a roadside breath-alcohol screening test (Alcolmeter SD-400) is negative [blood alcohol concentration (BAC) < 0.02 g/100 ml or 20 mg/100 ml] and there are indications of misuse of other drugs, then samples of blood and urine are obtained for toxicological analysis.

Administration of so-called standardized field-sobriety tests prior to arrest is not necessary in Sweden. It is the observations of the arresting police officers, the general appearance and behaviour of the driver and other indications that lead to suspicion and arrest for DUID. If toxicological analysis of blood samples subsequently proves negative there are no consequences or reprimands for the arresting police officers.

The police report contains details about the traffic stop and the driver's response to questions and whether any drugs or drug paraphernalia were observed. Examination of and the appearance of the person's eyes furnishes further clues about whether drugs might have been taken. Moreover, the police might have prior knowledge that the person used illicit drugs or had previous arrests for DUID and some suspects will readily admit that they had used illicit drugs. Examination of DUID offenders by specialist drug recognition experts (DRE) is not an option in Sweden.

A case-series of DUID ($n = 300$) was selected if amphetamine was the only psychoactive drug present in blood after completing a broad toxicological screening analysis and subsequent verification by more specific methods. The age and gender of the suspects was noted from the police arrest forms and compared with the concentration of amphetamine in blood. In a smaller retrospective sample ($n = 70$) the concentrations of amphetamine in blood were compared with the results of a clinical examination of the suspects made by a physician to assess drug-influence and impairment.

Determination of amphetamine in blood

Blood samples are taken from a cubital vein with Vacutainer tubes (2 × 10 ml) containing 100 mg sodium fluoride (NaF) and 25 mg potassium oxalate as preservatives. Efforts are also made to collect a specimen of urine (10 ml) in a tube containing NaF (1%) as a preservative. The urine and/or blood undergo a broad screening analysis for five classes of abused drugs (opiates, cannabinoids, amphetamine analogues, cocaine metabolite and certain benzodiazepines). The reagent used for amphetamine screening was enzyme multiplied immunoassay technique (EMIT)-amphetamine d.a.u. (Dade Behring Inc., Cupertino, CA, USA) and analysis was performed with an ADVIA 1650 instrument (Bayer Health Care Diagnostics, Tarrytown, NY, USA). All positive results from the screening analysis were verified by more specific methods [liquid chromatography-mass spectrometry (LC-MS or gas chromatography-mass spectrometry (GC-MS)]. Thus amphetamine was determined in blood by liquid–liquid extraction (ethyl acetate) at alkaline pH and the trifluroacetyl derivative was prepared before qualitative and quantitative analysis by GC-MS, with deuterium-labelled amphetamine as an internal standard [9].

The standard curve for determination of amphetamine was linear from 0.02 to 2.0 mg/l and the limit of quantitation (LOQ) of this method in routine use was 0.03 mg/l. When the concentration of amphetamine exceeded 2 mg/l the assay was repeated, starting with less blood (0.5 or 0.25 g) and adding drug-free blood to give approximately 1 g of starting material [9].

Although the aliquots of blood used for analysis were weighed, the concentrations of amphetamine are

reported here as mg/l to comply with international standards.

Clinical assessment of drug influence

A clinical examination of all DUID suspects was mandatory prior to introduction of the zero-limit law and results from such tests formed the main prosecution evidence. Apprehended drivers are first tested for alcohol influence with the help of a hand-held breath-alcohol instrument. This test is conducted at the roadside, and if other drugs are suspected the driver is transported to a police station and examined by a physician, who uses a test protocol developed originally to gather evidence of alcohol-impaired driving [10,11]. A retrospective material of DUID suspects ($n = 70$) from before the time of the zero-limit law was selected for evaluation, provided that amphetamine was the only drug present in the blood. The clinical examination comprised the following tests and items of information:

(i) Questions about general state of health, if any medication was being used and any recent consumption of alcohol or other drugs.
(ii) Physical appearance including height, weight, body size, clothes, obesity, colour of the face and pulse rate.
(iii) Examination of the eyes, whether bloodshot, watery, glassy, etc., as well as pupil size, reaction to light and presence of gaze nystagmus.
(iv) Ability to maintain balance, to walk straight, to walk and turn and the Romberg's test of ataxia.
(v) Simple measures of hand–eye coordination included finger-to-nose test, with both open and closed eyes.
(vi) The suspect's manner, whether anxious, nervous, calm, excited, talkative, elated, depressed or crying.
(vii) Orientation regarding time and place, knowledge of weekday, time of day and date.
(viii) Slurred speech was investigated by having suspects read a passage from a newspaper and to repeat complex words.
(ix) Simple cognitive ability was checked by counting backwards for at least 30 numbers starting at 107.

Finally, the physician had to decide whether the suspect was or was not under the influence of drugs other than alcohol and to what extent; that is, whether slightly, moderately or heavily influenced.

RESULTS

Blood amphetamine concentrations

Figure 1 shows a frequency distribution of the concentrations of amphetamine in blood samples from 300 DUID suspects when this stimulant was the only drug present. The distribution is skewed markedly to the right with mean, median and 2.5 and 97.5 percentiles of 1.0 mg/l, 0.9 mg/l and 0.06 and 3.0 mg/l, respectively. The highest concentration of amphetamine in blood was 7.1 mg/l.

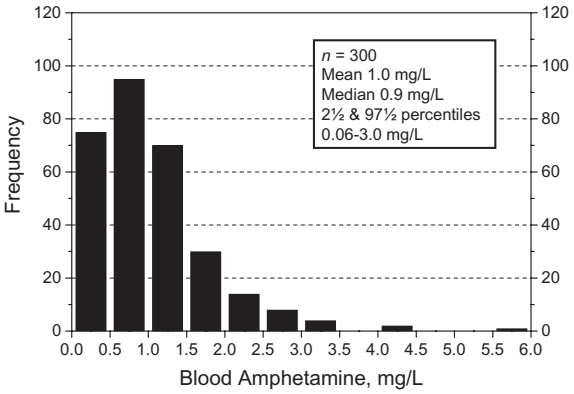

Figure 1 Frequency distribution of the concentrations of amphetamine in blood of people apprehended for driving under the influence of drugs (DUID) when amphetamine was the only drug present

Gender-related differences

Table 1 gives summary statistics of blood amphetamine concentrations in 300 DUID suspects, with the main focus on the age and sex of the offenders. The number of men dominated (82%), although no gender-related difference in their age was evident; men were 37.1 years (SD 8.7) and the women were 35.5 years (SD 7.1), with no statistically significant difference ($P > 0.05$). The women had slightly higher mean and median concentrations of amphetamine in blood; 1.11 mg/l (median 1.0 mg/l) versus 0.97 mg/l (median 0.8 mg/l), respectively; there were no statistically significant differences according to the Mann–Whitney test and Student's *t*-test ($P > 0.05$).

Age-related differences in blood amphetamine

The concentrations of amphetamine in blood tended to increase with increasing age of the DUID suspects, as shown by the scatterplot in Fig. 2. The correlation coefficient $r = 0.18$ was statistically significant ($P < 0.05$). The trend with age was easier to establish when the subjects were subdivided into seven age groups (Fig. 3). Both analysis of variance (ANOVA) and regression analysis verified a statistically significant increase in blood amphetamine concentration with advancing age ($P < 0.05$). When gender was introduced as an independent covariate along with age in a multiple regression analysis, the regression coefficient for gender –0.162 (SE: 0.124) was not statistically significant ($P > 0.05$).

Table 1 Summary statistics for age, sex and blood amphetamine concentrations in men and women suspected of drug-impaired driving in Sweden.

Sex	*n (%)*	*Age mean (SD)*	*Blood amphetamine (mg/l) mean (median) 2.5 and 97.5 percentiles*	*Blood amphetamine (mg/l) min and max values*
Male	246 (82)	37.1 (8.7)[1]	0.97 (0.8) 0.06–3.3	0.04–7.1
Female	54 (18)	35.5 (7.1)	1.11 (1.0) 0.05–2.8	0.04–2.8
Both	300 (100)	36.7 (8.5)	1.00 (0.9) 0.06–3.0	0.04–7.1

[1]No gender-related differences according to Student's *t*-test ($P < 0.05$) and the Mann–Whitney test.

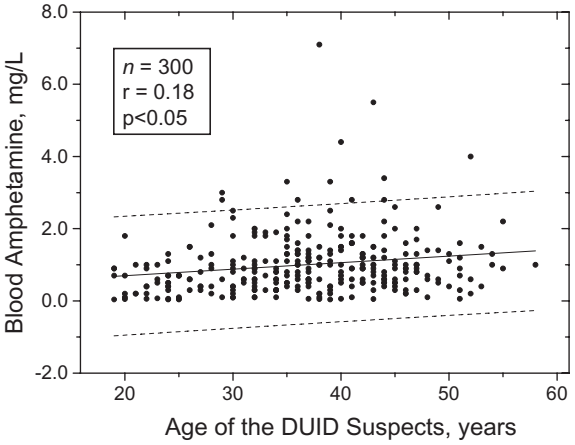

Figure 2 Scatterplot and correlation between the concentration of amphetamine in blood and the age of the DUID suspects

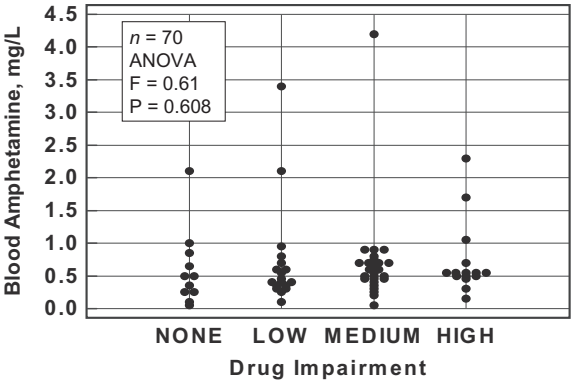

Figure 4 No relationship between concentration of amphetamine in blood and the degree of impairment according to the results of a clinical examination and questionnaire

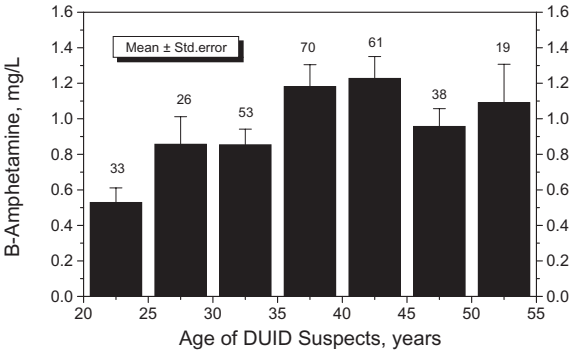

Figure 3 Association between the concentration of amphetamine in blood and the age of DUID suspects when subdivided into seven age groups

The corresponding coefficient for age was significant 1.86 (SE: 0.0056) ($P = 0.001$).

Signs of drug influence versus blood amphetamine concentration

The clinical examination and questionnaire were administered on average about 1 hour after the time of driving or after the police made the initial arrest. The physicians were aware that the people they were asked to examine were suspected of driving under the influence of alcohol or drugs.

The final conclusion from the clinical examination as to whether the suspect was not impaired (none), slightly impaired (low), moderately impaired (medium) or highly impaired (high) by drugs was plotted in Fig. 4 as a function of the concentration of amphetamine in blood. The concentrations of amphetamine within each impairment category showed much variation. To compare the four groups statistically, a logarithmic transformation was made to stabilize variances (Table 2). The ANOVA failed to disclose any differences in concentration of amphetamine between the different impairment categories ($P > 0.05$). A person with blood amphetamine as high as 2 mg/l was just as likely to be judged highly impaired as not impaired by this drug.

DISCUSSION

The introduction of zero-concentration limits in blood for controlled substances has greatly simplified the evidence necessary for a successful DUID prosecution [1–3]. Threshold concentrations of specific drugs are not written into the law because it is the LOQ of the analytical

Table 2 Blood amphetamine concentration arranged according to the results of a clinical examination of DUID suspects.

Impairment	*n*	*Blood amphetamine (mg/l) mean (median) conc.*	*Blood amphetamine (mg/l) min and max values*
None	11	0.60 (0.50)[1]	0.05–2.1
Slight	18	0.72 (0.43)[1]	0.1–3.4
Moderate	26	0.69 (0.57)[1]	0.05–4.2
High	15	0.73 (0.55)[1]	0.15–2.3

[1]No differences in mean concentration between groups according to one-way ANOVA after logarithmic transformation.

Table 3 Relationship between concentration of single drugs in the blood of motorists apprehended in Norway and the percentage of individuals judged impaired according to results of a clinical examination.

Drug	*n*	*Concentration of the drug in blood*	*Percentage of individuals judged impaired*
Ethanol	10 759	0.25–0.50 g/l	~73%
Diazepam	411	< 0.31 mg/l	~72%
Amphetamine	48	0.04–0.10 mg/l	~60%
THC[1]	80	< 0.0007 mg/l	~40%

[1]THC = tetrahydrocannabinol, the pharmacologically active metabolite of cannabis and marijuana.

method which determines whether a person is liable to prosecution for DUID. Because the LOQ is roughly 3.3 × limit of detection (LOD), the difference between the two thresholds creates a margin of analytical security for the accused.

The first Swedish DUID legislation, dating from 1951, required proof that the driver was impaired by a drug other than alcohol to such an extent that he or she was incapable of safe driving. This meant that all suspects were examined by a physician, who asked questions and conducted simple cognitive and psychomotor tests of impairment [11–13]. The results of these tests constituted the main prosecution evidence without which, regardless of the toxicology report, a conviction for DUID was not very likely [11,13]. Accordingly, many police authorities in Sweden lost interest in charging people with DUID unless a road-traffic crash had occurred, owing to the stringent requirements for a successful prosecution.

The present study failed to find an association between the degree of drug influence and the concentration of amphetamine in blood (Table 2 and Fig. 4). One reason for this stems from long-term use of stimulants and the development of acute and chronic tolerance [14,15]. Another major problem is that the concentration–effect relationship does not follow the concentration–time course of the drug in blood. Moreover, some people might be impaired and unfit to drive owing to exhaustion and fatigue from lack of sleep during an amphetamine binge. The concentrations of amphetamine in blood several days after use of the stimulant are likely to be fairly low compared with those existing shortly after administration.

A Norwegian study of DUID suspects with amphetamine as the only drug in blood reported that 73% were impaired and 27% were not impaired, according to results from a clinical examination [16]. Interestingly, the mean concentration of amphetamine in blood was about the same for the two classifications: impaired (0.53 mg/l) and not impaired (0.50 mg/l). Such high concentrations of amphetamine indicate abuse of the stimulant and toxicological analysis of blood samples furnishes more useful information in this respect compared with a clinical examination.

The notion of establishing science-based concentration limits for amphetamine or other illicit drugs has been advocated by some investigators based in part on the results of clinical tests of impairment [16–20]. The results from such tests are summarized in Table 3, where surprisingly large percentages of those tested were judged impaired, despite fairly low and insignificant concentrations of ethanol, diazepam, amphetamine and Δ^9-tetrahydrocannabinol (THC) in blood [20]. For example, approximately 73% of 10 000 individuals were judged impaired at BAC between 0.25 and 0.5 g/l (25–50 mg/100 ml). Note that the legal blood alcohol limit for driving in Norway is 0.2 g/l (20 mg/100 ml) compared with 0.80 g/l (80 mg/100 ml) in the United Kingdom, the United States and Canada, which confirms that politics rather than science determines the *per se* alcohol limits for driving.

The low concentrations of amphetamine and THC in blood (Table 3) make it hard to understand how 60% and 40%, respectively, of those examined could be considered impaired. Similarly, 72% of people with low therapeutic

concentrations of diazepam in blood (< 0.31 mg/l) were impaired, a finding that might astonish many clinical pharmacologists [21–23]. People prescribed this anxiolytic develop tolerance after a few days of treatment and thereafter do not necessarily exhibit signs and symptoms of drug influence or impairment [24,25]. However, it is important to note that tolerance shows large individual variations and thus might not mean that regular users of diazepam are safe drivers [24].

The high proportions of people judged impaired at such low concentrations of alcohol and other drugs in blood (Table 3) suggests that some kind of bias has crept into the clinical examination of DUID suspects. The physicians concerned are certainly aware that the people examined have passed or failed a roadside breath alcohol test. Some physicians might be more motivated or better trained than others, or more desirous of reaching a conclusion of drug-related impairment, considering the circumstances under which such testing is performed.

The lack of a control group of subjects without any drugs in blood is also a serious drawback in the evaluation of these studies. Moreover, it is common knowledge that people who are sober might react strangely when confronted by the police becoming anxious or nervous, which might raise a suspicion of drug influence. Various medical conditions, nervousness, fatigue, sleep-loss or psychiatric disorders are likely to be construed as being indicative of using drugs and thus undermine the validity of clinical tests of impairment.

The above criticisms also apply to the results of the present study (Fig. 4), where there was no association between blood amphetamine concentration and the degree of drug influence. Such clinical tests are designed to detect signs and symptoms of drug influence, which might or might not bear a relationship to skills related to driving. Case–controlled studies of the risk of a crash after taking drugs other than alcohol have not yet been reported. Another example of bias in the clinical assessment is that many suspects admit to use of illicit drugs—they name the drug, when last used, the dose and the route of administration. In general, clinical testing of DUID suspects and a medical questionnaire are below the standard required for good experimental design in medical research [26]. This calls for caution and reservations when the results of such testing are interpreted.

The mean and median concentrations of amphetamine in blood of 6613 DUID suspects, most of whom were polydrug users, were 0.89 mg/l and 0.70 mg/l, respectively, compared with 1.0 mg/l (mean) and 0.9 mg/l (median) in the 300 cases reported here with amphetamine as the only drug present. The mean age of the amphetamine users was 37 years and the concentrations in blood increased slightly with advancing age, although there were no sex-related differences. Interestingly, DUID suspects with amphetamine as the only drug present were about 10 years older compared with users of GHB (mean 26.0 years, $n = 29$) or cannabis misuse (mean 25.4 years, $n = 136$) (unpublished work). Those DUID suspects taking amphetamine have probably had a long experience with this central stimulant and have developed an appreciable tolerance to its effects [27,28].

CONCLUSIONS

The lack of a relationship between the concentration of amphetamine in blood and the degree of drug influence according to the results of a clinical examination and medical questionnaire speaks against the notion of setting threshold concentrations in blood or enacting graded penalties depending on the level determined. Some evidence exists to support a science-based legal limit for THC in blood, although the concentration will probably have to be set fairly high [29–31]. Enactment of threshold concentration *per se* limits for stimulants such as amphetamine lack equivalent scientific support [16–19]. It is a myth to believe that drunk-driving laws are science-based, considering that punishable blood concentrations in different countries differ widely (20–80 mg/100 ml). Zero blood concentration limits or LOQ limits represent a much more pragmatic way to enforce DUID legislation.

The introduction of such zero-tolerance laws for DUID has not deterred drug-impaired drivers and recidivism is very common among these traffic delinquents [1]. Since the zero-limit law came into force, the police in Sweden have undergone special training to help them recognize typical signs and symptoms of drug influence. This has evidently proved very effective, judging by a more than 10-fold increase in the number of blood samples sent for toxicological analysis. This reflects, among other things, stronger motivation to proceed with a charge of DUID armed with the knowledge that a successful prosecution is more or less guaranteed if a controlled substance is identified in blood. The traditional effect-based or impairment-based DUID laws are ineffective because of the development of tolerance and the weak dose– and concentration–effect relationships for many drugs. Without an unequivocal diagnosis of drug impairment there would be little chance of winning a conviction for DUID if the case went to trial.

Acknowledgements

This line of research was supported in part by a grant from the Milan Valverius foundation.

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