Morphine Blood Concentration and Clinical Impairment in a Population of Drugged Drivers

L Bachs¹
J Bramness¹
S Skurtveit²
JMørland¹

Norwegian Institute of Public Health, ¹Division of Forensic Toxicology and Drug Abuse and ²Division of Epidemiology, P.O. Box 4404 Nydalen, N-0403 Oslo, Norway. liba@fhi.no

Background
The study of the consequences of opiate use in traffic is complex. The medical and illicit use of opioids has been recognised to constitute a potential traffic hazard [1,2,3,4]. Some countries have recently introduced per se laws against the use of morphine among drivers. Analytical epidemiological studies for all opiates as a group have shown low relative risks, often not statistically significant [5,6,7,8]. For morphine alone there is some support for risk in experimental performance studies [9,10] as well as in analytical epidemiological studies [8].

Norway is a country with a high prevalence of detected drugged driving [11]. In cases of suspected drugged driving, a blood sample is drawn from the suspect shortly after the incident that caused the suspicion. At the same time a physician performs a Clinical Test for Impairment (CTI) according to a fixed protocol. Blood samples and CTI results are sent together to the Norwegian Institute of Public Health, Division of Forensic Toxicology and Drug Abuse in Oslo for analysis and further evaluation. The Division of Forensic Toxicology analyses and interprets the results from the all blood samples from suspected drugged drivers in Norway. This gave us the access to a large number of suspected drugged driving cases involving morphine. The aim of this study was to see if the concentration of morphine alone had any correlation to the outcome of the CTI. For this purpose, we selected samples that contained morphine only and not any other drug, and compared the analytical results on blood morphine with the conclusions from the accompanying CTI.

Objectives
The aim of our study was to investigate the influence of morphine blood concentration on a Clinical Test for Impairment (CTI) performed in relation to suspected drugged driving.

Methodology
All the present data were taken from an existing database at the Norwegian Institute of Public Health. This database contained analytical results from blood samples sent by the police in cases of suspected drugged driving counting approximately 21700 cases for the years 1999 to 2003. The database was searched for positive blood morphine results.

Analytical methods: All blood specimens that had been analysed on the suspicion on drugged driving during the period 1999 to July 2001 had routinely been screened respectively confirmed for ethanol with ADH and GC methods, for opiates, high dose benzodiazepines (e.g. diazepam, nitrazepam, oxazepam), amphetamine, cocaine and tetrahydrocannabinol with EMIT II immunological tests. Confirmatory analysis and drug concentration measurements had been performed by GC/MS and GC-ECD. Other screening analyses for drugs not included in the standard screening program had been
performed if the police suspected certain drugs, or if impairment was concluded by the CTI and the impairment could not be explained by the results from the standard set of analyses. The most common drugs looked for in these extended analytical programs were low-dose benzodiazepines (flunitrazepam, clonazepam, alprazolam, midazolam) and muscle relaxants (carisoprodol/meprobamate). The analytical procedures and cut-off values have been previously described elsewhere [11] [12].

For the blood specimens analysed during the period August 2001 to 2003, the standard screening program had been extended to routinely include screening and confirmatory analysis performed by LC-MS for all the afore mentioned benzodiazepines as well as carisoprodol, meprobamat, methadone, phenobarbital, carbamazepine, zopiclone, zolpidem and dextropropoxyphene.

Morphine, codeine and ethylmorphine were quantified by gas chromatography (GC). The detection limits were 8 ng/ml for codeine, 8 ng/ml for ethylmorphine and 9 ng/ml for morphine.

Clinical test for impairment: In all the cases of suspected drugged driving, the police request the collection of a blood and urine sample as well as a CTI performed by a physician, as soon as possible after the incident that led to suspicion. The time elapsed between the incident and the performance of the CTI varied widely, but was most commonly around 2 hours, while the collection of the blood sample always took place in close conjunction with the CTI. The CTI consisted of three elements: 1) A short drug history, 2) a set of tests to be completed with an accompanying conclusion on impairment, 3) an evaluation of other possible reasons for impaired driving (disease, etc.). The set of tests was composed of 23 different single tests that evaluated psychomotor and physical performance as well as the level of consciousness. The conclusion of the CTI made by the physician was reached without any particular written guidelines and was stated as “impaired” or “not impaired”. The CTI report form was sent to our Institute together with the blood sample.

Morphine blood concentration groups: Morphine concentrations were categorised in either low, moderate, medium or high: Concentrations in the range 9-14 ng/ml (7 cases) were referred to as “low”. This range of concentrations can be expected shortly after a dose of 2.5-5 mg morphine or heroin intravenously. Concentrations in the range 15-29 ng/ml (45 cases) were referred to as “moderate”. This range of concentrations can be expected shortly after a dose of 5-10 mg morphine or heroin intravenously. Concentrations in the range 30-59 ng/ml (38 cases) were referred to as “medium”. This range of concentrations can be expected shortly after a dose of 10-20 mg morphine or heroin intravenously. Concentrations in the range 60-85 ng/ml (8 cases) were referred to as “high”. This range of concentrations can be expected shortly after a dose of 20-30 mg morphine or heroin intravenously.

Statistical methods: Statistical analyses were based on chi-square tests for categorical variables and Students t-test or non-parametrical Mann-Whitney test for continuous variables using Statistical Package for Social Sciences (SPSS) version 10.1. Differences between groups were studied using ANOVA.

Results and Analysis
Morphine was present in the blood samples of approximately 2000 cases analysed between 1999-2003. The majority (92 %) of these morphine positive cases, contained other drugs in combination with morphine, mostly benzodiazepines. Morphine only, was
found in 168 (8%) of the samples. Of the 168 cases, 70 did not fulfil criteria for further analysis because there was no CTI report (57) or because CTI was inconclusive (13). The rest of the cases, 98, were subject for further analysis.

**Analytical findings:** Mean morphine concentration was 31 ng/ml (median 27, SD 16, range 9-85). Frequencies of various blood concentrations measured are shown in figure 1.

**Concentration and impairment:** Of the 98 cases, 21 (21%) were described as “not impaired”, while 77 (79%) were stated as “impaired” based solely on the conclusion from the physician on the report form. In the impaired group 40 (52%) were evaluated as “mildly impaired”, 27 (35%) as “moderately impaired” and 10 (13%) as “highly impaired”.

Mean blood morphine concentration in the “not impaired” group was 34 ng/ml (median 30 ng/ml, SD 19). Mean concentration in the “impaired” group was 31 ng/ml (median 27 ng/ml, SD 15). There was not a statistical significant difference between the two groups (fig 2. left panel).

![Blood morphine concentrations distribution](image1.png)

**Fig. 1** Blood morphine concentrations distribution

![Box plot of morphine concentrations in subjects judged as not impaired and impaired](image2.png)

**Fig. 2.** Box plot of morphine concentrations in subjects judged as not impaired and impaired. Previous results for codeine are shown for comparison.
Morphine concentrations were further categorised as low, moderate, medium or high. Number of subjects judged as impaired showed no significant difference between concentration groups with a tendency towards fewer impaired subjects at the higher concentration groups (71%, 82%, 79% and 62% respectively) (fig 3). Previously published data on codeine [13] is shown in fig. 2. and 3 together with morphine data for comparison.

Discussion and Conclusions
This data suggests a considerable number of impaired subjects for all concentration levels in the range found in this group of apprehended drivers. We cannot see any correlation between blood morphine concentration level and number of impaired subjects in our material. Such correlation has previously been described in a population of drugged drivers for another opioid, codeine, and for benzodiazepines and carisoprodol/meprobamate [13,14]. Others have shown correlation between morphine dose/ blood concentration in a similar range and impairment measured by different psychomotor tests in healthy volunteers [9,15].

We did not find a significant blood morphine concentration difference between the group judged as “impaired” and the group judged as “not impaired”. A priori, several factors as opiate acute and chronic tolerance and low CTI sensitivity would generally suggest a low degree of apparent impairment in a study like ours [16]. Even though all subjects in this study were included due to suspicion by the police of being impaired, it was a surprising high percentage of the drivers which were judged as impaired even at very low blood morphine concentrations. We have previously investigated codeine concentration – effect relationships in a similar population, and found a lower percent of impaired cases at lower blood codeine concentrations (fig 3) as well as a significant difference in mean blood codeine concentration between drivers judged as impaired and drivers judged as not impaired (fig 2 right panel). Tolerance is not, however, the only relevant pharmacodynamic phenomenon in repeated morphine use. Depending on the interval between doses, also sensitisation (eg. Increased effect to the same concentration or dose) to morphine effects has been reported from animal studies [17, 18]. It is tempting to use both tolerance and sensitisation to explain our findings. A high prevalence of sensitized subjects could explain the frequent finding of clinical impairment at low concentrations and a somewhat lower prevalence of tolerant subjects could explain that many passed the test as not impaired with high concentration of morphine in their blood. Another explanation may be related to morphine metabolites that were not analyzed in our samples. Morphine 6-glucuronide has been shown to have analgesic properties as well as increasing

![Fig. 3. Percent of subjects impaired at different concentration](image-url)
locomotion in mice. It has recently been reported that repeated heroin use increases the formation of the active metabolite morphine 6-glucuronide and reduces the formation of the inactive morphine 3-glucuronide both in animals and humans [19, 20]. A large interindividual variation in the ratio morphine to 6-morphine glucuronide in heroin users may have contributed to obscure the relationship between morphine blood concentration and clinical impairment, while the concentration-effect relationship for total active opiates could still have been present.

Possible next steps
- A more detailed study of the CTI findings and the relation between impairment and different population characteristics as age and gender may contribute to enlighten our results.
- A further study of the morphine to morphine 6-glucuronide ratio in our population is a possible next step. The correlation between the blood concentration of 6-morphine glucuronide and degree of impairment should be elucidated.
- An experimental study on the sensitisation to morphine psychomotor effects in humans would also be a possible approach.

Reference List


