Impairment Due to Intake of Carisoprodol

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Background
The current presentation includes material from a previously published study [1]. Carisoprodol is a centrally acting muscle relaxant prescribed for a variety of muscle tension problems, but mostly for lower back pain [2]. The drug is metabolized to an active metabolite meprobamate [3-5], which had a more widespread use as an anxiolytic and hypnotic in the 60-ties and 70-ties.

Driving under the influence of non-alcoholic drugs is an increasing problem in Norway [6], also when medicinal drugs are concerned [7]. CNS-depressants have gained special attention for their ability to reduce driving ability and increase risk of accidents [8-10]. Driving under the influence of carisoprodol has been noted as a problem [11, 12].

In Norway drivers suspected of driving under the influence of non-alcoholic drugs are examined by a police physician shortly after apprehension. This is done by a 25 item Clinical Test of Impairment (CTI25) [13]. Together with this examination a blood sample is drawn. The examination results and blood sample are sent together to the Norwegian Institute of Public Health, Division of Forensic Toxicology and Drug Abuse for analysis. Over the years this activity has generated a substantial database. Many of the apprehended drivers have blood drug concentrations far above what could be expected after a therapeutic drug intake [14], also when carisoprodol is concerned [11]. We thus had the opportunity to study some effects of supratherapeutic intake of carisoprodol, a phenomenon impossible to study in controlled trials due to ethical considerations.

Objectives
In the present study we wanted to address the possible impairing effects of carisoprodol in apprehended drivers. This was done by relating the blood drug concentrations of carisoprodol and the metabolite meprobamate with impairment as measured by CTI25.

Methodology
All the data in the present study were taken from an existing register, containing data on all apprehended, suspected drugged drivers in Norway. The register contains approximately 140,000 analytical results from drivers suspected of DUI from the years 1987-2002. During this period meprobamate was not available as a medicinal drug on the Norwegian market, and its detection in a blood sample was therefore a consequence of its biotransformation from carisoprodol. Cases selected for this study were those where meprobamate was detected alone or together with its parent drug carisoprodol. 62 cases contained only meprobamate mostly together with its parent drug carisoprodol, but no other drugs. These cases constituted our material. The researchers handled these cases anonymously.

The Norwegian version of CTI (CTI25) consists of a short interview where apprehended drivers are asked about drinking habits and drug history as well as present intake, followed
by 25 observations and tests, including 7 tests on alertness, cognitive function and vestibular function, 4 observations on eyes, 2 observations on cardiac action, 4 tests of motor activity/coordination and 8 observations concerning appearance [13]. The CTI25 ends with the conclusion whether the apprehended driver is “not impaired” or “impaired” [15].

All blood samples received at the institute were routinely screened for alcohol by an enzymatic method and common drugs of abuse (amphetamines, benzodiazepines, cannabis, cocaine and opiates) by enzyme immunoassays [6, 16]. In some cases blood samples were screened for additional drugs of abuse by a gas chromatography or a liquid chromatography/mass spectrometry method. Drugs like antidepressants, opioids, antiepileptics and barbiturates where detected by these methods. All positive results were eventually confirmed by gas chromatography modified as described elsewhere [6].

For statistical analysis the drug concentrations were grouped as “lower concentrations” or “mildly” or “highly elevated”. The mildly and highly elevated concentration groups could represent drug levels above what would be expected after therapeutic intake of carisoprodol.

Data analyses were performed using Statistical Package for the Social Sciences (SPSS) version 11.0. Levels of significance for all statistical analysis were set to $P < 0.05$ (*), $P < 0.01$ (**) or $P < 0.001$ (***)

**Results**

When moving from one blood carisoprodol concentration group to the next, an increasing portion of the suspected drivers where judged impaired by the physician (Fig. 1). When dividing the drivers according to blood meprobamate concentration only those with a mildly elevated blood meprobamate concentration differed from the lower blood meprobamate concentration. These findings were replicated in a binary logistic regression model and the relationship withstood adjustment for other variables (data not shown). The exception for this was that the relationship between meprobamate and impairment did not withstand adjustment for the blood carisoprodol concentration.

Several of the test and observations of the CTI25 related to blood carisoprodol concentration. These included subdued consciousness, abnormality of the eyes, horizontal gaze nystagmus, Romberg’s test positive, abnormal gate and turning on line, abnormal finger-to-nose test, faulty counting backwards, abnormal articulation, incoherent speech, abnormality of face and facial expression, involuntary movements, hand tremor and abnormal general conduct. Only subdued consciousness related to blood meprobamate concentration.
**Figure 1** Percentage of apprehended drivers determined “impaired” at different drug levels. The subjects (N=62) were grouped according to blood carisoprodol and meprobamate concentrations. The number of drivers in each group is depicted on the low end of the column concerned. Groups were compared pair-wise using $\chi^2$-test. Fewer drivers were judged impaired in the group with carisoprodol below detection limit than in the groups with elevated carisoprodol (a). Fewer drivers were judged impaired in the group with lower carisoprodol than in the group with highly elevated carisoprodol (b). Fewer drivers were judged impaired in the group with lower meprobamate concentrations than in the group with mildly elevated meprobamate (c). * P < 0.05 and *** P < 0.001. DL = detection limit.

Discussion
We found a concentration effect relationship between blood carisoprodol concentration and impairment as measured by the physician’s conclusions to the CTI25. The same relationship was not found for blood meprobamate. Furthermore, many of the subtests and observations of the CTI25 related positively to blood carisoprodol concentration while this occurred only for one observation and blood meprobamate concentration.

Earlier research has failed to show an impairing effect after the intake of 700 mg carisoprodol [17], but effects have been demonstrated after the intake of larger doses [18]. The blood carisoprodol concentrations reached after intake of 700 mg carisoprodol may not be sufficient to demonstrate the impairing effects of carisoprodol.

Carisoprodol is metabolized to meprobamate [4, 5]. Carisoprodol has a terminal elimination half-life 1.5 hours, compared to 8-16 hours for meprobamate [19]. Regular intake of carisoprodol may thus accumulate meprobamate, but not carisoprodol. This could give rise to of tolerance towards the impairing effects of meprobamate. Furthermore, it could make difficult on a group level to differentiate between meprobamate...
present in the blood samples due to recent or chronic intake of carisoprodol. The blood drug concentrations of the two drugs are highly related, however, due to its shorter terminal elimination half-life, carisoprodol could act as an indicator of recent meprobamate elevation. The present relationships between blood carisoprodol concentration and impairment may thus be specific to carisoprodol per se or an effect of recent meprobamate elevation due to intake of carisoprodol.

In the present study we therefore applied different strategies in order to entangle whether the relationship between blood carisoprodol concentrations and impairment was due either to a specific effect mediated by carisoprodol itself or if the effect of carisoprodol is mediated through its metabolite meprobamate, but with carisoprodol as an indicator.

Impaired occasional users of carisoprodol had both higher blood carisoprodol and meprobamate concentrations than not impaired drivers. For regular users of carisoprodol (with accumulation of meprobamate), such a difference was only found for blood carisoprodol concentration. The impairing effects of meprobamate are well known [20], and the present findings does not undermine such effects. It is not possible however to establish if there were separate impairing effects of carisoprodol from our findings keeping in mind the above-mentioned argument about accumulation of meprobamate and tolerance towards the impairing effects of meprobamate in regular users of carisoprodol.

Blood carisoprodol concentration and blood meprobamate concentration are highly dependent variables. Nevertheless, the regression model applied in the present study did indicate that the impairing effects of carisoprodol were more pronounced than the impairing effects of meprobamate.

Many of the clinical effects of carisoprodol were similar to what we have observed for benzodiazepines [13]. It is reasonable to believe that meprobamate works as an agonist to the barbiturate site on the GABA_A-receptor complex and hence the clinical effects of meprobamate should resemble those of benzodiazepines. However, there were some effects found in the present study that cannot be attributed meprobamate or agonist action towards the GABAergic receptor complex. These include tachycardia, involuntary movements, hand tremor and possibly horizontal gaze nystagmus.

Case reports of carisoprodol intoxications point to similar to clinical features. In these case reports effects of probably highly elevated carisoprodol concentrations are described and include shivering, myoclonus and tachycardia.

The CTI25 is used as the dependant variable in the present study. The sensitivity of the CTI25 in revealing impairment may be low, but may be adequate for clinical settings. We have little knowledge of the reliability of the CTI25. The consequences of this has been reviewed elsewhere [15]. Furthermore we have scant knowledge of the dose ingested and time of ingestion for the apprehended drivers. All these factors could have had implications for the present results. However, as these limitations potentially would obscure a concentration-effect relationship, and since such a relationships in fact was found, one could argue that our findings represent rather robust phenomena. Thus the concentration-effect relationship and the clinical effects specific to carisoprodol found in the present study are likely to be consistent.

As for many other drugs there are obviously great interindividual differences in the impairment due to a certain blood carisoprodol concentration. Even so, the present findings indicate that this variability is not of an extent to totally obscure a concentration-
effect relationship. We have shown this earlier also with benzodiazepines [15], opening for a discussion on legal limits for benzodiazepines and driving. The present findings point to a similar relationship for carisoprodol, supporting that caution should be observed when prescribing carisoprodol to drivers.

References