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The involvement of prescribed drugs in road trauma

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ABSTRACT

Coroners files and toxicological records of fatally-injured drivers in Victoria from 2000 to 2006 and from 2007 to 2013 were reviewed in separate studies to establish the role of prescribed drugs on crash risk. 2638 driver fatalities were included in the study, which represented over 97% of all driver fatalities in this period. The detection limits of the drugs were at the low end of those seen with common illicit drugs or prescribed drugs. Drugs of any type were found in 34.4% of the study group, medicinal drugs 21.2%, and alcohol (≥0.05 gram/100 mL) was found in 24.8%. The prevalence of the most common drugs detected that are legally available by prescription were anti-depressants (7.9%), benzodiazepines (7.0%), opiates/opioids (6.6%), and sedating anti-histamines (1.1%). Each driver was assessed for responsibility using a previously published and validated method. The crash risk of drivers taking opioids, benzodiazepines, or anti-depressants (primarily the serotonin reuptake inhibitors), were not significantly over-represented compared to the drug–free control group, although there was a suggestion of increased crash risk for benzodiazepines. Crash risk was elevated for drivers using cannabis (by presence of THC in blood at > 2 ng/mL) and amphetamines. These data show that drivers using medicinal drugs alone are unlikely to show significant crash risk even if drugs are potentially impairing.

1. Introduction

Drug use on Australian roads and their link to increased crash risk was first reported in a large scale multi-center retrospective study [1]. This showed that after alcohol cannabis and amphetamine-type stimulants (ATS) were most associated with an elevated crash risk. A validated culpability analysis of each crash was conducted using records obtained from the state coroners' offices [2].

Since this report other studies using the same or similar culpability analyses have confirmed the elevated crash risk associated with recent cannabis use and ATS. Positive detection of THC in blood (>1 ng/mL) was associated with a significant increased risk of responsibility (odds ratio, OR 3.3) when over 10,000 fatally-injured drivers in France were studied even after adjustment for possible confounding factors. A significant dose effect was also identified [3]. Similarly, recent use of cannabis was also associated with an increased crash risk (OR 4.6) in 900 injured drivers compared to drug-free control drivers [4]. A meta-analysis of all relevant studies has confirmed that THC is associated with an elevated crash risk [5].

Victoria has been proactive in the enforcement of illegal drugs in driving for well over 10 years using both an impairment model [6] and random roadside testing on oral fluid [7,8]. However, there are a number of other drugs used by drivers involved in fatal collisions. These include narcotic analgesics (opiates and opioids), anti-depressants, benzodiazepines, and sedating anti-histamines.

Elevated crash risk has been shown with use of benzodiazepines (OR 1.7) in injured drivers [4]. Similar trends were also observed in an Australian study [9]. Most population-based case control studies and other types of epidemiological designs have shown a modest increase in crash risk for benzodiazepines, particularly the longer half-life forms, and confirmed using meta-analyses particularly in maintaining proper road lateral position [10–19].

Tricyclic antidepressants are known to impair primarily due to their sedative side effects, however the reuptake inhibitors now dominate this area of medicine and provide less sedative activity [20]. Estimations of crash risk using various types of approaches have not given consistent results [14,16,17,21]. Hence there is still some doubt as to whether they contribute to any measureable

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increase in crash risk and any change could be more due to symptoms of the disease than actual drug-caused crash risk [22].

The effect of opiates is even less apparent and again variable estimations of crash risk have been obtained from elevated to no increase [1,4,12,17,21]. More recently truck drivers using opioid analgesics have been shown to have a moderate increase in unsafe driver behavior [23].

Since the use of responsibility analysis can provide a measure of any association between drug presence and crash risk, two studies were commissioned to examine the extent of prescription drug involvement in fatal collisions in Victoria over a 14-year period. This manuscript describes the results of these two studies in relation to crash risks of medicinal drugs.

2. Materials and methods

2.1. Study population

The study population consisted of drivers killed in motor vehicle accidents in Victoria using data were obtained from records kept at the Victorian Institute of Forensic Medicine and the State Coroners Office. From 2000–2006 drivers were identified on the basis of records obtained from the State Coroners court following permission of the State Coroner. From 2007 to 2013 the National Coronial Information System (NCIS) was used to identify driver fatalities. This database contained records of the police report to the coroner which detail the circumstances of the crash, as well as providing copies of the autopsy and toxicology reports, and coronial findings.

In Victoria all driver fatalities had blood collected for a full toxicological investigation irrespective of type or cause of death. Only cases that were on-road motor vehicle crashes were included. Crashes that occurred off-road, or those that were classified as natural or suicide were excluded. When a death occurred in hospital, specimens analyzed from relevant ante-mortem specimens were used in the analysis. A proportion of cases were excluded where toxicology was not conducted due to unavailability of specimens, specimens were collected more than 3 h after the crash or where the file did not contain sufficient information for culpability analyses.

2.2. Drug Analysis

Toxicology testing is routine in all cases and included testing for alcohol, drugs of abuse (ATS, benzodiazepines, cannabinoids, cocaine, opiates) using Cedia® immunoassay kits, and included chromatographic screens with either GC-MS or tandem LC-MS for a large range of common prescription and over-the-counter drugs capable of impairing such as analgesics, opioids, anti-depressants, sedating anti-histamines and anti-psychotics (latter mainly since 2006) [24,25]. Detection limits for all drugs were at least at the low end of their therapeutic range for prescription drugs and at the low end of blood concentrations commonly seen for illicit drugs (ATS, heroin and its metabolites, cocaine and its metabolites).

All drugs detected were confirmed and quantified in preserved leg blood by appropriate mass spectrometric techniques (GC-MS and LC-MS/MS). Cannabis testing was based on the presence of Δ^9-tetrahydrocannabinol (THC) using a cut-off of 2 ng/mL. Non-sedating antihistamines were not detected by the analytical methods used in the laboratory. Alcohol was detected and confirmed using conventional GC methods using a reporting limit of 0.01 gram/100 mL.

Drugs administered to the deceased post-crash as part of medical treatment were excluded from consideration. This information was obtained from medical records either held within the coroner's brief or other records that formed part of the death investigation.

2.3. Categorization of drugs

To simplify the statistical analysis of drug-effects, drugs were categorized into drug families. All substances acting as stimulants were placed into the ATS group. This included amphetamine, methylamphetamine, 3,4-methylenedioxy-methylamphetamine (MDMA), ephedrine, pseudoephedrine, phentermine and cocaine. All benzodiazepine drugs were placed into this drug group including the related drugs zolpidem and zopiclone. The opioid group included morphine, 6-acetylmorphine (6-AM), codeine, fentanyl, methadone, meperidine (pethidine), oxycodone and tramadol. The cannabinoid group only included cases found to contain THC in blood above a detection limit of 2 ng/mL. All drugs were placed into drug groups based on their pharmacological classification, i.e. anti-histamines, anti-psychotics, anti-depressants. The database allowed a distinction to be made for sub-types such as cyclic and serotonin (and mixed) reuptake inhibitors anti-depressants.

2.4. Responsibility analysis

The responsibility analyses were performed as per published method [2] with results from an earlier period published elsewhere [1]. The basis of responsibility analysis was to determine the responsibility of drivers after a review of eight mitigating factors in the absence of knowledge of the involvement of drugs in the crash or the presence of drugs in the body fluids of the deceased. These mitigating factors were: condition or road, condition of vehicle, driving conditions, type of crash, witness observations, road law obedience, and difficulty of task and level of fatigue. An index of responsibility was then established using predetermined scoring guidelines based on the sum of the eight scores for each factor. Drivers were then grouped into one of three categories–culpable (culpability score <13), contributory (≥ 13 and ≤ 15) or non-culpable (>15). The proportion of drivers who were culpable to those not culpable was then calculated for various drug groups including the drug-free group. This proportion was called the culpability ratio. Cases found to be contributory were not included in the statistical analyses. The results of the toxicological examination were added to the database only after the responsibility analysis had been completed. The alcohol and drug-free driver represented the control group.

The odds ratio (OR) was calculated for drivers in the various drug groups by dividing the culpability ratio for the treatment group by the culpability ratio for the control group.

2.5. Statistical analyses

Statistical analysis for assessing differences in culpability ratios between groups (unadjusted) was conducted using Chi Square or Fisher's Exact test, depending on the size of the sample. Statistical significance was determined at $\alpha = 0.05$.

2.6. Ethics approvals

The project was approved by the Victorian Institute of Forensic Medicine ethical review process (RAC 27/14) and by the Department of Justice Ethics committee (CF/14/24349) for access to the NCIS for 2007–2013 cases.

3. Results and discussion

3.1. General data

All driver fatalities identified were included in the dataset, which represented in number 97% of the known driver deaths in