Traffic accident risk associated with the prescription of drugs: a review of seven Norwegian registry-based cohort studies

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Abstract

Background

There is limited information about traffic accident risk associated with using medicinal drugs. We aimed to summarize seven Norwegian studies about the traffic accident risk after dispensing prescribed drugs. Different medicines were studied, including those where an increased traffic accident risk would be expected, as well as drugs without any such expectations.

Methods

Information on prescriptions and traffic accidents were obtained from population-based registries. The Norwegian population aged 18-69 between January 2004 and September 2006 was studied (3.1 million people). The Norwegian Road Accident Registry and the Norwegian Prescription Database were coupled based on the unique identification number assigned to all individuals living in Norway. The drug exposure period was defined as the first week after the day of dispensing the drug. Standardized incidence ratios (SIR) were calculated by comparing the incidence of accidents among subjects prescribed the drug in question with the incidence among unexposed subjects.

Results

During the study period 20,494 road accidents with personal injuries occurred. The accident risk was in general highest for men, and higher for the younger ages. The road traffic accident risk was increased for those who had received prescriptions for any medicine (SIR for both genders combined = 1.4; 95% CI: 1.3-1.5). About the same SIRs were found for subjects exposed to antidepressants and NSAIDs. The risk was further increased for subjects exposed to natural opium alkaloids (2.0; 1.7-2.4), methadone (2.1; 1.4-3.1), non-benzodiazepine hypnotics (2.3; 2.0-2.7) and tranquilizing- (2.9; 2.5-3.5) and hypnotic (3.3; 2.1-4.7) benzodiazepines.

Conclusion

Confounding factors related to the state of needing prescribed drugs may have played a role in this study. The increased risk of traffic accidents for subjects prescribed drugs with abuse and sedating potential, supports results from previous studies, and did in particular represent new knowledge related to the commonly used medicines zopiclone and codeine.
Background

It is well documented that driving under the influence of alcohol leads to traffic-relevant impairment (Schnabel, Hargutt & Krüger, 2010) and implies an increased risk of involvement in traffic accidents (Blomberg, Peck, Moskowitz, Burns & Fiorentino, 2009). Even though driving under the influence of non-alcohol drugs has been less studied than driving under the influence of alcohol, there is evidence that certain non-alcohol drugs may have a similar traffic deteriorating effect as alcohol (Vindenes et al., 2012). To reach this conclusion, different study designs have used unlike aspects of traffic relevant impairment as end-points (Mørland, 2000). The majority of these studies have concerned drugs with a potential for abuse, e.g. cannabis, opioids and benzodiazepines.

Epidemiological studies on traffic accident risk related to driving under the influence of prescribed drugs demand systematic collections of large numbers per medicinal drug of interest. Since 2004, Norway has had a national database covering all prescriptions dispensed outside hospitals (Furu et al., 2010). By connecting these data with the national database of road traffic accidents, it is possible to find the relationship between prescribed medicines and traffic accident involvement for the Norwegian population. So far, seven such studies on different medicinal drugs have been published (Engeland, Bramness, Mørland & Skurtveit, 2007; Bramness, Skurtveit, Mørland & Engeland, 2007; Gustavsen et al., 2008; Bachs, Engeland, Mørland & Skurtveit, 2009; Bramness, Skurtveit, Mørland & Engeland, 2012; Bramness, Skurtveit, Neutel, Mørland & Engeland, 2008; Bramness, Skurtveit, Neutel, Mørland & Engeland, 2009).

Aims

We aimed to summarize the results from the seven population-based Norwegian publications on road traffic accident risk among drivers being exposed to prescribed medicines.

Methods

Registries

All studies have coupled data from three Norwegian population-based registries: the Central Population Registry (NCPR), the Norwegian Road Accident Registry (NRAR) and the Norwegian Prescription Database (NorPD). The NRAR contains information about drivers involved in road traffic accidents with personal injuries. Information about the blame apportioned to drivers was not available. The NorPD captures only prescriptions outside hospital and does not contain any information on when the dispensed medicines were used.

Data handling

All citizens registered in the NCPR aged 18-69 years (3.1 million) were coupled to the NRAR to identify drivers who had been involved in traffic accidents during the time period April 2004 to September 2005 (Engeland et al., 2007; Bramness et al., 2007) or April 2004 to September 2006 (Gustavsen et al., 2008; Bachs et al., 2009; Bramness et al., 2008; Bramness et al., 2009; Bramness et al., 2012). The data files were thereafter coupled to the NorPD. The drivers were stratified by gender and in ten age-groups (due to the age at January 1st 2005).

Standardized Incidence Ratio (SIR)
The incidence of accidents in the exposed person-time was compared with the incidence of accidents in the unexposed person-time by calculating the SIR (and 95% confidence interval (CI)). In nearly all papers, we assumed that the drivers used the drug the first week after dispensing it from the pharmacy, i.e. exposed person-time was defined as the first seven days starting at the date after dispensing the drug. Multiple exposure periods were allowed to each person, but only one accident (the drivers were excluded after being involved in a road traffic accident).

Any additional co-prescriptions were allowed for the results shown here. For a more comprehensive view of the calculations, see the original papers. The SIR for incident use after a 180 days of wash-out period was calculated for: antidepressants, codeine, zopiclone, carisoprodol and diazepam.

Results

Table 1  Standardized incidence ratio (SIR) and a 95% confidence interval (CI) for the first seven days1 after dispensing a drug in the drug group in question.

<table>
<thead>
<tr>
<th>Drug groups</th>
<th>Accidents (N)</th>
<th>SIR (95% CI)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opium alkaloids</td>
<td>114</td>
<td>2.0 (1.5-2.5)</td>
<td>2.0 (1.5-2.6)</td>
</tr>
<tr>
<td>Benzodiazepine tranquillizers</td>
<td>140</td>
<td>3.1 (2.5-3.8)</td>
<td>2.7 (2.1-3.6)</td>
</tr>
<tr>
<td>Benzodiazepine hypnotics</td>
<td>27</td>
<td>4.1 (2.6-6.2)</td>
<td>1.7 (0.6-4.0)</td>
</tr>
<tr>
<td>Sedating antidepressants</td>
<td>204</td>
<td>1.4 (1.2-1.7)</td>
<td>1.5 (1.2-1.8)</td>
</tr>
<tr>
<td>Non-sedating antidepressants</td>
<td>884</td>
<td>1.6 (1.4-1.7)</td>
<td>1.6 (1.5-1.8)</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>101</td>
<td>1.6 (1.2-2.1)</td>
<td>1.5 (1.0-2.0)</td>
</tr>
<tr>
<td>Penicillins</td>
<td>44</td>
<td>1.4 (1.0-2.0)</td>
<td>0.7 (0.4-1.2)</td>
</tr>
<tr>
<td>Any prescribed drug</td>
<td>977</td>
<td>1.4 (1.3-1.5)</td>
<td>1.3 (1.2-1.4)</td>
</tr>
</tbody>
</table>

1For sedating and non-sedating antidepressants the calculations were based on the number of days corresponding to the number of defined daily doses (DDDs) prescribed.

The 3.1 million included persons were involved in 12,865 road traffic accidents until September 2005 and 20,494 accidents until September 2006. The accident risk was in general higher for the younger age-groups compared to the older (results not shown).
Table 1 shows the risk of being involved in a traffic accident for groups of medicines and table 2 for certain specific drugs. The risks shown in Table 1 and 2 were in general higher for men than for women. Table 1 shows an increased road traffic accident risk related to benzodiazepines or opium alkaloid exposure. Exposure to any prescribed medicines gave a moderately increased SIR, quite similar to what was found for antidepressants, NSAIDs and penicillins (for men).

Table 2 Standardized incidence ratio (SIR) and a 95% confidence interval (CI) for the first seven days after dispensing the drug in question.

<table>
<thead>
<tr>
<th>Prescribed drug</th>
<th>Accidents (N)</th>
<th>SIR (95% CI)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carisoprodol</td>
<td>66</td>
<td>4.0 (2.7-5.6)</td>
<td>3.6 (2.5-5.0)</td>
</tr>
<tr>
<td>Methadone</td>
<td>23</td>
<td>2.4 (1.5-3.6)</td>
<td>1.1 (0.2-3.1)</td>
</tr>
<tr>
<td>Codeine</td>
<td>181</td>
<td>2.0 (1.6-2.4)</td>
<td>1.8 (1.4-2.3)</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>129</td>
<td>2.5 (1.9-3.1)</td>
<td>2.2 (1.7-2.8)</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>21</td>
<td>2.4 (1.2-4.3)</td>
<td>2.0 (1.0-3.7)</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>27</td>
<td>2.8 (1.7-4.5)</td>
<td>2.4 (1.1-4.6)</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>18</td>
<td>4.9 (2.7-8.0)</td>
<td>2.2 (0.5-6.4)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>72</td>
<td>2.9 (2.1-3.9)</td>
<td>2.6 (1.8-3.8)</td>
</tr>
</tbody>
</table>

Table 2 shows a clearly increased road traffic accident risk related to carisoprodol, diazepam, nitrazepam or zopiclone exposure. For methadone and flunitrazepam the risk was significantly increased for men only, which may be explained by a low exposed person-time for these drugs. Exposure to zolpidem or codeine gave moderately increased SIRs. The SIR was not increased after exposure to lithium or valproate (Bramness et al., 2009) (results not shown).

Incident use lead to the following SIRs (both genders combined): sedating antidepressants: 1.0 (0.7-1.4), nonsedating antidepressants: 1.6 (1.3-1.9), carisoprodol: 1.9 (0.7-4.1), diazepam: 3.3 (1.6-5.8), zopiclone: 2.1 (1.3-3.1) and codeine: 1.1 (0.7-1.5).

**Discussion and conclusions**

We found that the risk of being involved in an accident as a driver was slightly increased in users of prescribed drugs in general, and substantially increased in users of benzodiazepines and opioids; in particular related to carisoprodol, codeine, zopiclone, zolpidem, nitrazepam and diazepam. The risk was in general highest for men and the younger ages.
Strengths of this method were that the entire Norwegian population (3.1 million) was included, and that a good data quality was ascertained by using population-based registries.

We had no information about whether (or when) the prescribed medicines were taken. There may have been factors related to the need of prescribed medicine leading to an increased traffic accident risk other than, or in addition to, the drug itself, e.g. that the disease itself may have increased the risk (confounding by indication). Further, the group of patients who receive prescriptions of benzodiazepines or opioids, or psychiatric patients, may tend to use more alcohol and narcotic drugs compared to healthy individuals (Lader 2011; Mordal, Bramness, Holm & Mørland 2008.) We had no information about possible use of alcohol, narcotic drugs and non-prescribed medicines. Other studies on road traffic accident risk point to a particular group of individuals being at the highest risk, consisting of young men who probably represent a risky behavior including excessive alcohol, narcotic and drug use (Legrand et al., 2013). The SIRs in this study also demonstrated higher risks for younger men which to some degree may support the assumption of a marginalized group of people being at the highest risk. However, the increased accident risk related to certain medicinal drugs was in accordance to former studies on traffic accident risk that have used other study designs (Legrand et al., 2013; Dassanayake, Michie, Carter & Jones, 2011), which supports the usefulness of this study design and confirms a particular risk connected to these medicines. For the commonly prescribed drugs zopiclone and codeine, this setup revealed new knowledge.

A somewhat lower SIR was found for incident use after 180 days of washout for antidepressants, codeine, zopiclone and carisoprodol, but not for diazepam. This may be explained by a low degree of tolerance for all drugs except for diazepam. More likely, these results may have been disturbed by a selection bias: persons who receive the prescription infrequently differ from those who receive it often.

Our conclusion is that patients should be warned against driving the first 1-2 weeks after receiving a prescription of psychoactive drugs.

References


