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Road traffic crash risk associated with prescription of hydroxyzine and other sedating H1-antihistamines: A responsibility and case-crossover study

Ludivine Orriols[a,*], Audrey Luxcey[a], Benjamin Contrand[a], Anne Bénard-Laribière[b], Antoine Pariente[b,c], Blandine Gadegbeku[d,e,f], Emmanuel Lagarde[a]

[a] Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team IETO, UMR 1219, F-33000 Bordeaux, France
[b] Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARCOEPIDEMIOLOGY, UMR 1219, F-33000 Bordeaux, France
[c] CHU Bordeaux, Service de Pharmacologie Médicale, F-33000 Bordeaux, France
[d] Université de Lyon, F-69000 Lyon, France
[e] IFSTTAR, UMR T 9405, UMRESTTE, F-69500 Bron, France
[f] Université Lyon 1, UMRESTTE, F-69000 Lyon, France

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ABSTRACT

Background: H1 antihistamines differ from each other by their ability to cross the blood-brain barrier. The resulting sedating effect can be sought in therapy but may be a driving hazard. The aim of this study was to estimate the impact of sedating H1-antihistamines on the risk of road traffic crash, with a particular focus on hydroxyzine which is also indicated as an anxiolytic in France.

Methods: The study consisted in extracting and matching data from three French nationwide databases: the national healthcare insurance database, police reports and the police national database of injurious crashes. All sedating H1-antihistamines, including hydroxyzine, were considered in the study. A case-control analysis, in which responsible drivers were cases and non-responsible were controls was performed. A case-crossover analysis, comparing for the same subject exposure during a period immediately before the crash with exposure during an earlier period, was also conducted.

Results: The extraction and matching procedures over the July 2005-December 2011 period led to the inclusion of 142,771 drivers involved in an injurious road traffic crash. The responsibility study found an increased risk of being responsible for an injurious road traffic crash in hydroxyzine users who were registered with a long-term chronic disease (mostly psychiatric disorders) on the day of the crash (OR = 1.67 [1.22–2.30]). Among them, the risk was even higher in drivers with highest exposure levels (OR = 2.60 [1.23–5.50]). There was no impact of sedating H1 antihistamine treatment initiation on the risk of crash.

Conclusion: Even if it is difficult to disentangle the part of the increased risk that would be causally related to hydroxyzine and the part related to behaviours of patients with a heavy psychiatric disorder, our study raises the alarm on the crash risk linked to hydroxyzine utilization in countries in which the anxiolytic indication is widespread.

1. Introduction

Histamine exerts diverse biologic effects through four types of receptors. H1 and H2-receptors are widely expressed, in contrast to H3 and H4- receptors. Antihistamines are a class of medicines that block the action of histamine at the H1-receptor sites (H1- antihistamines) or at the H2-receptor site (H2 antihistamines). H2 antihistamines are used to treat gastrointestinal conditions, acting upon H2-receptors located in the gastrointestinal tract. H1 antihistamines down regulate allergic inflammation mainly through the H1-receptor which is widespread in smooth-muscle and neurons. H1 antihistamines are commonly classified according to function of first-generation, which are sedating, as compared with second-generation which are relatively nonsedating. These H1 antihistamines differ from each other by their ability or not to cross the blood-brain barrier, which determines the presence of sedative central effects. The importance of sedation (reduction of daytime alertness, slight drowsiness or deep sleep) varies according to the degree of blood-brain barrier crossing and to the relative affinity of H1-antihistamines for peripheral and central receptors.

A review of 16 double-blind studies versus placebo involving

* Corresponding author at: Injury Epidemiology, Transport, Occupation Team, Centre INSERM U1219 “Epidémiologie Et Biostatistique” Université De Bordeaux, Case 11, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France.
E-mail address: ludivine.orriols@isped.u-bordeaux2.fr (L. Orriols).

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different antihistamines and using driving tests in healthy volunteers concluded that first-generation antihistamines significantly impair driving performances after both single dosing and repeated daily administration. Second-generation antihistamines may also affect driving abilities after single-dose administration, to a lesser extent and especially with higher dosages (Verster and Volkerts, 2004). A limited number of epidemiological studies have investigated the impact of antihistamines on the risk of road traffic crash. In the studies by Leveille et al. and by Ray et al., both conducted in the elderly, the association was not significant (Leveille et al., 1994; Ray et al., 1992). However, these findings should be interpreted cautiously as they could result from a lack of statistical power. Howard et al. showed that histaminergic consumption was associated with the risk of traffic crashes in professional drivers (Howard et al., 2004). This result, in a particular population, is very difficult to extend to a general driving population. In a more recent case-series study, the use of antihistamines for more than four weeks was associated with motor vehicle crash, but shorter term use was not (Gibson et al., 2009). The authors noted however that it was unlikely that they had complete exposure data on these medicines. Finally, a case-control study found that second-generation antihistamines may have a protective effect against traffic crashes (Perttula et al., 2014).

The sedative effect can sometimes be sought in therapy but is most often a limiting side effect for driving or operating machinery. Among the sedating H1-antihistamines, hydroxyzine, apart from its use in allergy, may also be indicated as an anxiolytic. This indication is however not recommended in all countries. While the anxiolytic use of hydroxyzine is common in France (Zahreddine and Richa, 2013) and Spain (Sanchez et al., 2013), it is not the case in the UK and Ireland (British National Formulary,2017). To our knowledge, no epidemiological study investigated the specific impact of hydroxyzine on the risk of crash. However, Tashiro et al. showed that subjects taking hydroxyzine had significantly slower brake reaction time than those given fexofenadine (Tashiro et al., 2005).

The aim of this study was to provide further insights into the impact of sedating H1-antihistamines on the risk of road traffic crashes, with a particular focus on hydroxyzine.

2. Methods

We extracted and matched data from three French nationwide databases: the national healthcare insurance database (SNIIR-AM), police reports (PRs) and the police national database of injurious crashes (ICs). Drivers were included by means of their national healthcare ID number (NID), extracted from PRs by an automatic procedure. PRs were matched to records in the IC database by a probabilistic linkage method (Orriols et al., 2010) (Fig. 1). Responsibility in the crash was determined to conduct a case-control study in which responsible drivers were cases and non-responsible were controls. The NID was used to link drivers to medicine reimbursement data around the crash date. Exposure to H1 antihistamines was estimated from dispensing dates.

2.1. Ethics statement

Confidentiality was ensured by using the personal information anonymization function of the healthcare insurance system (Trouessin and Allaert, 1997).The study was approved by the French Data Protection Authority.

2.2. Data sources

2.2.1. Police reports (PRs)

French police forces are required to fill out a PR for each injurious crash occurring in the country (about 70 000 reports each year). PRs are scanned and stored as image files. For some of the drivers involved in these injurious road traffic crashes, the NID is recorded in the PR. A previous validation study showed that the NID was recorded for 28% of the drivers involved (Orriols et al., 2010). These NIDs were extracted from PR image files for later matching against dispensing records in the SNIIR-AM database. All PRs available over the study period (from July 2005 to December 2011) were compiled.

2.2.2. National police database of injurious crashes (IC database)

Police personnel collect details on injurious road traffic crashes and store in this database all information about the crash, vehicles, and persons involved. They also conduct investigations from hospital records about the severity of the driver's injuries: unhurt, slightly injured, and seriously injured (hospitalized > 24 h), or killed (died within 30 days following the crash). All drivers involved in an injurious road traffic crash must be tested for the presence of alcohol, using a breath test. If this test is positive ($\geq$0.5 g/L), or the driver refuses the test, or the severity of the crash makes it impossible to administer the test, then the driver's blood alcohol concentration is measured. If the breath test is negative, the driver is recorded as not being under the influence of alcohol.

2.2.3. National healthcare insurance database (SNIIR-AM)

The SNIIR-AM database covers the entire population of France. A record is added each time a reimbursed prescription medicine is dispensed to an outpatient at a pharmacy, including national ID number, date of dispensing, and the seven-digit code that identifies medicines. Data on long-term chronic diseases are also recorded in this database, together with the ICD-10 code (International Classification of Diseases, Tenth Revision) as well as the start and end dates of the disease. In France, patients are fully reimbursed for healthcare expenses related to 30 recognized long-term chronic diseases.

2.3. Participant inclusion

A driver was excluded if the police report did not contain his or her national ID or if the extraction procedure failed or a link could not be established with the corresponding record in the national police database of injurious crashes. If a driver was involved in several crashes during the study period, only the first crash was considered, to ensure that the dispensing of a drug was not a consequence of a previous crash.

2.4. Medicines and exposure periods

Medication exposure was considered to start on the day following dispensing. To ensure that medicines were not prescribed as a consequence of the crash, medicines dispensed on the crash day were not considered.

Exposure duration was estimated from median values reported in a survey on medicine prescription in France. This survey was conducted among 800 practitioners, representative of French physicians, three times a year, over a 7-d period, during which all prescriptions were collected (IMS Health, 2005-2011).

2.4.1. Antihistamines

Sedating antihistamines. All H1-antihistamines approved for reimbursement by the French health authoriries were considered, that is 1/sedating H1-antihistamines: hydroxyzine, phenothiazine derivatives (alimemazine, mequitazine, oxomemazine, promethazine), substituted alkylamines (brompheniramine, dexchlorpheniramine), piperazine derivatives (oxatomide, meclozine and combinations), aminoalkyls ethers (carbinoxamine, doxylamine and combinations) and other antihistamines for systemic use (ketotifene, mizolastine, rupatadine); 2/ non-sedating antihistamines: H1-antihistamines from the R06 ATC class, excluding sedating antihistamines listed above.

Special attention was paid to hydroxyzine, approved for both antiallergic and anxiolytic properties in France. The maximum recommended dose for hydroxyzine is 100 mg per day. Complementary