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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Drug dependence associated with triptans and ergot derivatives: a case/non-case study

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Abstract
Introduction The aim of this case/non-case study was to assess and compare the risk of drug dependence associated with different migraine-specific drugs, i.e., ergot derivatives and triptans, using the French pharmacovigilance database.
Methods Reports on drug side effects recorded in this database between January 1985 and June 2007 were analyzed, and triptans (almotriptan, eletriptan, naratriptan, sumatriptan, and zolmitriptan) as well as ergot derivatives used in acute migraine were examined. For all reports, cases were defined as those reports corresponding to "drug abuse," "physical or mental drug dependence," and "pharmacodependence," whereas "non-cases" were defined as all the remaining SED reports. The method's reliability was assessed by calculating the risk associated with a negative (amoxicillin) and a positive (benzodiazepines) control. The risk of dependence associated with each drug and control was evaluated by calculating the odds ratio (OR) with a confidence interval of 95%.
Results Among the 309,178 reports recorded in the database, drug dependence accounted for 0.8% (2,489) of the reports, with 10.9% (449) involving a triptan, and 9.33% (332) an ergot derivative. The risk of dependence was similar for triptans and ergot derivatives and did not differ from that of benzodiazepines. In the triptan group, the risk (odds ratio [95% CI]) ranged from 10.3 [4.8–22.3] for sumatriptan to 21.5 for eletriptan [10.1–45.6], while in the ergot derivative group, it ranged from 12 [8–17.9] for ergotamine to 20.6 [8–53] for dihydroergotamine.
Conclusions These findings confirm the hypothesis that triptans and ergot derivatives are associated with an increased risk of drug dependence.

Keywords Migraine treatment · Medication overuse · Drug dependence · Triptans · Ergot derivatives · Case/non-case study

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Introduction

Acute migraine affects about 11% of the Caucasian population [1], and it is treated with common analgesics or specific drugs, such as ergot derivatives and the more recently available triptans [1]. Medication-overuse (MO) has been associated with the use of analgesics, opioids [2–4], ergot derivatives [5], and more recently, with triptans [2, 3, 6–10]. MO is a secondary cause of chronic daily headache occurring in 4% of the population worldwide [11] and 3% of the French population [12]. Medication-overuse headache (MOH) is defined by the following criteria: headache present at least 15 days a month, regular intake (≥10 days per month for >3 months) of one or more anti-

migraine drugs, occurrence or worsening of headache during medication overuse, and reversion to the previous pattern within 2 months after discontinuation of the overused medication [13]. MOH, whose physiological mechanism is suggested to be similar to that of drug addiction [14, 15], is mentioned in the summary of product characteristics for anti-migraine drugs as "headache secondary to excessive use," "daily chronic headache secondary to excessive use," or "headache or rebound secondary to chronic use." MOH has been associated with the use of opioids, ergot derivatives, and triptans [2–4]. Case reports pertaining to MOH were published shortly after the launch of sumatriptan [9, 16], naratriptan, eletriptan, and zolmitriptan [10, 17]. MOH may share characteristics with drug dependence [9]; the latter is defined [18] as a maladaptive pattern of substance use, leading to clinically significant impairment or distress manifested by one or more of seven criteria (Table 1). Several of these criteria, i.e., tolerance, withdrawal, and overuse ("taking the substance often in larger amounts or over a longer period than was intended"), are closely related to those of MOH. In an observational study involving 1,861 patients with chronic daily headache, 48% were identified as MOH patients, and among these, 68% met drug dependence criteria [19].

No epidemiological study so far has compared the different migraine-specific drugs in terms of drug dependence risk using a case/non-case study design.

Aim

The aim of our study was to assess and compare the risk of drug dependence associated with different classes of anti-migraine drugs.

Methods

A case/non-case study design was used, based on the side effects of drugs (SED) recorded in the French pharmacovigilance database.

Since 1985, all SED reports sent spontaneously by health professionals, but not manufacturers, to 1 of the 31 French Regional Pharmacovigilance Centers have been entered into this database. Before being recorded in the database, each SED report is reviewed by medically qualified personnel at the center. Irrespective of their severity, all SEDs recorded in the French pharmacovigilance database from January 1, 1985, to June 17, 2007, were included in the analysis. *Cases* were defined as SED reports that contained at least one term indicative of drug dependence according to the database's glossary, i.e., "physical drug dependence," "mental drug dependence," "pharmacodependence," or "drug abuse." Although MOH did not exist in the database's glossary, "drug abuse" was deemed to be a close description of MOH. *Non-cases* (controls) were all the remaining SED reports recorded in the database. Exposure to one of the study drugs was defined as an SED report where one of the study drugs was mentioned and had the highest imputability score. Because of the potential occurrence of multiple SEDs within the same report, one patient could appear in both cases and non-cases. However, since the case group was very small compared to the non-case group, the impact was not considered significant.

Case/non-case studies [20, 21] based on database data rely on principles similar to case/control studies. This method may be used to generate signals from a pharmacovigilance database [21, 22]. It is based on the principle that the number of SED reports recorded with all drugs remains

Table 1 Diagnostic criteria for substance dependence. Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV)

Criteria
Tolerance, as defined by either of the following:
The need for markedly increased amounts of the substance to achieve intoxication or desired effect
Markedly diminished effect with continuous use of the same amount of the substance
Withdrawal, as manifested by either of the following:
The characteristic withdrawal syndrome for the substance
The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
Taking the substance often in large amounts or over a longer period than was intended
A persistent desire or unsuccessful efforts to cut down or control substance use
Spending a great deal of time in activities necessary to obtain or use the substance or to recover from its effects
Giving up social, occupational, or recreational activities because of substance use
Continuing the substance use with the knowledge that it is causing or exacerbating a persistent or recurrent physical or psychological problem

The DSM IV defines the diagnostic criteria for substance dependence as a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by one or more of the above, occurring within a 12-month period

Table 2 Risk of drug dependence associated with triptans, ergot derivatives, benzodiazepines, and amoxicillin

	All adverse events (a+c)	Drug dependence (a)	OR [95% CI]
Triptans	449	49 (10.9%)	15.38 [11.4–20.74]
Zolmitriptan	212	23	15.2 [9.8–23.4]
Sumatriptan	91	7	10.3 [4.8–22.3]
Naratriptan	84	10	16.7 [8.6–32.4]
Eletriptan	54	8	21.5 [10.1–45.6]
Almotriptan	8	1	17.61 [2.2–143.2]
Ergot derivatives	332	31 (9.33%)	12.84 [8.85–18.62]
Ergotamine	297	26	12 [8–17.9]
Dihydroergotamine	35	5	20.6 [8–53]
Benzodiazepines	11,093	649 (5.8%)	10 [9.13–10.96]
Amoxicillin	17,311	1 (0.005%)	0.01 [0–0.5]

a Drug dependence adverse events associated with the study drug, *a+c* all adverse events associated with the study drug, *OR* odds ratio

constant over time although the proportion of a given SED recorded with a specific drug may exceed the expected value. The association between drug exposure and SED was assessed by calculating the relative risk (RR), also called proportional reporting ratio [20, 21]. As the number of drug dependence cases is much lower than the total number of SED reports recorded in the database, the relative risk may be evaluated by calculating the odds ratio (OR).

The study drugs were those labeled in France for migraine attacks: triptans, i.e., almotriptan, eletriptan, naratriptan, sumatriptan, and zolmitriptan; and ergot derivatives, i.e., oral ergotamine and inhaled or injectable dihydroergotamine. The reliability of the method was assessed by calculating the risk associated with a negative control (amoxicillin, which has never been linked to drug dependence) and a positive control (benzodiazepines, for which the risk of drug dependence is well established) [23].

For the analysis, the total number of SEDs irrespective of the drug used (n) and the number of drug dependences associated with all drugs (a+b) were assessed. For each study drug, the number of drug dependences associated with the study drug (a), the number of drug dependences associated with all drugs except the study drug (b), the number of SEDs other than drug dependence associated with the study drug (c), the number of SEDs other than drug dependence associated with all drugs except the study drug (d), and the total number of SEDs associated with the study drug (a+c) were assessed.

This data was either obtained directly from the database (n, a, a+b, a+c) or calculated (b, c, d).[1] The risk of drug dependence for each anti-migraine drug and each control (amoxicillin and benzodiazepines) was determined by calculating the odds ratios (OR = ad/bc) with 95% confidence intervals [21].

[1] $b = (a + b) - a; c = (a + c) - a; d = n - (a + b) - c$

Results

Among the 309,178 SED reports recorded in the French pharmacovigilance database from January 1, 1985, to June 17, 2007, 2,489 drug dependences were reported accounting for 0.8% of all reports. There were 449 SED reports involving triptans, with drug dependence occurring in 10.9% (49 reports), and 332 SED reports involving an ergot derivative, with drug dependence occurring in 9.33% (31 reports).

The risk of drug dependence was similar for triptans (OR=15.38 [11.4–20.74]) and ergot derivatives (OR=12.84 [8.85–18.62]), and for both drugs, the risk was found not to differ from that of benzodiazepines (OR=10 [9.13–10.96]). In contrast, the risk of drug dependence for amoxicillin was almost zero (OR=0.1 [0–0.5]). The drug dependence risk among the triptans ranged from 10.3 [4.8–22.3] for sumatriptan to 21.5 [10.1–45.6] for eletriptan, and among the ergot derivatives from 12 [8–17.9] for ergotamine to 20.6 [8–53] for dihydroergotamine (Table 2). The accuracy of the result for almotriptan is limited since there was only one report of drug dependence associated with this drug.

Discussion

Our results indicate that the use of ergot derivatives and triptans was associated with a risk of drug dependence.

To our knowledge, the present study is the first of its kind to use a case/non-case design to estimate the risk of drug dependence. For the purpose of our study, this method was deemed reliable for analyzing drug dependence because we found no particular risk associated with amoxicillin (negative control) but a high risk associated with benzodiazepines (positive control). The case/non-case design is a suitable method for conducting internal comparisons to detect associations between specific SEDs and drug exposures. The method is simple, quick, and

cheap, and uses data already available. The problems associated with the recruitment of controls for case/control studies do not apply to case/non-case studies, for all reports not identified as cases are non-cases. Several studies using the case/non-case method have been published on this database applying to different fields of drug safety [24–26]. One limitation of the pharmacovigilance database and consequently of the case/non-case method [20, 26] lies in the selection and notoriety bias due to the spontaneous notification system, which depends on the cooperation and goodwill of healthcare professionals [25–28]. The association between a given drug and an SED may be artificially decreased if another specific SED is more often reported (and inversely, the association may be increased if there are only a few other SEDs associated with the study drug). Finally, if several drugs that are likely to induce a specific SED are used concomitantly, this SED may be observed among both cases and non-cases [26]. However, since concomitant use of triptans and ergot derivatives is contra-indicated, this bias is unlikely to have occurred in our study.

The results of the present paper using the case/non-case method confirm that the use of ergot derivatives and triptans was associated with a risk of drug dependence. Previous studies have assessed MOH or headache recurrence more often than drug dependence, and the incidence of overuse more often than its risk. In one study of 1,720 triptan consumers, 4% used these drugs more than 10 times a week [29], and in another study of 20,686 triptan consumers, 1.9% took them more than 12 times a month [30]. In a French study, 8% of 301 patients treated with triptans reimbursed by the national health insurance system took these drugs more than 12 times a month [31], and hence could be considered to be overusers. Data from 53 trials [32] involving triptans suggested that the risk of headache recurrence might be lower for frovatriptan, naratriptan, and eletriptan, which display a longer half-life than the other available triptans. As headache recurrence promotes drug overuse, which is a risk factor for drug dependence, it may be hypothesized that the risk of drug dependence might be lower for these three drugs. However, our data cannot be used to support this theory linking dependence to triptans to their respective half-lives, since the 95% intervals were very large and overlapped.

A few other studies have addressed the issue of dependence to acute migraine treatments. A marked need for a substance, similar to that which addicts experience for drugs, has been observed in chronic daily headache patients overusing analgesics [33]. The authors hypothesize that this dependence is not due to the addictive properties of analgesics, but to their capacity to alleviate the patient's suffering in spite of daily headache. In a series of patients suffering from probable MOH in Taiwan, 68% of the subjects met the criteria of substance dependence [19], with most of them (80%) overusing ergotamine. In a multicenter, cross-sectional, observational study conducted in France, 66.8% of MOH patients were considered dependent on acute headache treatments according to DSM IV criteria [34]. A significantly higher number of dependent versus non-dependent MOH patients were found to have overused opiate-containing acute headache treatments, and both dependent and non-dependent MOH patients (with no statistical difference found between both groups) often overused triptans, whereas only a few of them overused ergotamine. In another publication, 60% of the subjects suffering from pure triptan-overuse headache fulfilled criteria of drug dependence compared to 79% of those suffering from combined (triptan and other anti-migraine drugs) overuse headache [35].

In our analysis, no difference was found between triptans and ergot derivatives concerning risk of drug dependence, although some authors previously observed that with ergotamine overuse, there was lower incidence [5], a more rapid occurrence (1.7 vs 2.7 years) [13, 36], a lower monthly intake frequency [36], and a shorter time to recovery upon treatment cessation (5 vs. 10 days) [37] than with triptan overuse. This discrepancy in results may be accounted for by the longer observation period (1985–2007) of the current study. In fact, a decrease in ergotamine overuse was noted since triptans were launched on the market. In the United States, ergotamine overuse decreased from 19% in 1990 to 0% in 2005, whereas triptan overuse increased from 0% to 22% during the same time period [38].

Conclusion

Our findings support the hypothesis that triptans and ergot derivatives are associated with an increased risk of drug dependence. The study results also demonstrate the usefulness of applying the case/non-case method to a large pharmacovigilance database to reveal a link between a given drug and a side effect as guidance for confirmatory prospective studies.

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