Risk of ischemic complications related to the intensity of triptan and ergotamine use

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Neurology 2006;67;1128-1134
DOI: 10.1212/01.wnl.0000240128.76399.fa

HIGH LIGHT
CME

Risk of ischemic complications related to the intensity of triptan and ergotamine use

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Abstract—*Objective:* To investigate whether the intensity of triptan and ergotamine use, in specific overuse, is associated with the risk of ischemic complications. *Methods:* We conducted a retrospective nested case-control study using data from the PHARMO Record Linkage System. All patients with more than one prescription for either a triptan or ergotamine were initially identified. Cases were all patients who were admitted to the hospital for an ischemic complication. Matched controls were assigned the same index date as the cases. The determinant was the intensity of use of triptans and ergotamine during 1 year preceding the index date. Overuse was defined as use of ≥90 defined daily doses during that year. Conditional logistic regression was used to estimate odds ratios (ORs), adjusting for confounders. Stratified analysis was used to estimate the risk for both patients using and those not using cardiovascular drugs. *Results:* A total of 17,439 patients received more than one prescription. A total of 188 cases and 689 controls were identified. Triptan overuse was not associated with an increased risk of ischemic complications (OR 0.96; 95% CI: 0.49 to 1.90). Overuse of triptans in patients concomitantly using cardiovascular drugs did not increase this risk. Overuse of ergotamine turned out to be a risk factor for ischemic complications (OR 2.55; 95% CI: 1.22 to 5.36). Patients overusing ergotamine and concomitantly using cardiovascular drugs were at highest risk (OR 8.52; 95% CI 2.57 to 28.2). *Conclusions:* In general practice, triptan overuse does not increase the risk of ischemic complications. Overuse of ergotamine may increase the risk of these complications, especially in those simultaneously using cardiovascular drugs.

NEUROLOGY 2006;67:1128–1134

The ergot alkaloids were the first specific antimigraine therapy available. Intermittent, chronic, and excessive use of ergotamine can lead to serious ischemic adverse effects such as peripheral ischemia, arterial stenosis, myocardial infarction, and cerebral ischemia,[1-3] probably due to its broad pharmacologic activity involving serotonin ($5HT_1$ and $5HT_2$), dopamine, and α-adrenoceptors. Sumatriptan and the other second-generation serotonin $5HT_{1B/1D}$-receptor agonists (triptans) have improved the quality of acute migraine treatment by providing a higher degree of efficacy and a more favorable side effect profile vs ergotamine. However, due to their $5HT_1$ agonist activity, triptans can also cause coronary, craniovascular, and peripheral vasoconstriction possibly leading to serious complications such as myocardial infarction,[4-7] ischemic stroke,[8,9] and ischemic colitis,[10-12] mostly in patients with cardiovascular disease or risk factors. Therefore, the use of triptans, like ergotamine, is contraindicated in these patients.

The incidence of ischemic complications is extremely low when triptans are used appropriately.[13-16] However, some patients use triptans more frequently than recommended, which may lead to medication overuse headache (MOH).[17] One study examined the relationship between the intensity of triptan and ergot alkaloid use and the risk of stroke, but found no dose-response relationship.[16] However, the overall intensity of use in this study was low and no category of overuse was defined. It remains unclear whether overuse of triptans or ergot alkaloids is associated with an increased risk of ischemic events.

Therefore, we conducted a retrospective nested case-control study to investigate whether the intensity of triptan and ergotamine use, in specific over-

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Disclosure: The authors report no conflicts of interest.

Received March 31, 2006. Accepted in final form July 17, 2006.

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use, is associated with the risk of serious ischemic complications that require hospitalization.

Methods. *Setting.* We received data from the PHARMO Record Linkage System, which includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of all 950,000 community-dwelling residents of 25 population-defined areas in The Netherlands from 1985 onward.[18] Because virtually all patients in The Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription drugs. Participants of the PHARMO population enter the database with the first prescription filled in a PHARMO community pharmacy and are followed until the last prescription.

The computerized drug-dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dose regimen, and the estimated duration of use. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Patient information per prescribed medicine includes gender and date of birth. The database does not provide information concerning the indications for use of the medicines, in this case, the diagnosis of migraine vs cluster headache, or accurate registration of nonprescription medicines (e.g., use of over-the-counter salicylates, nonsteroidal anti-inflammatory drugs [NSAIDs], paracetamol).

The hospital discharge records were obtained from the Dutch Medical Register (LMR) from PRISMANT, an institute that collects all hospital discharge records nationwide in The Netherlands since the 1960s in a standardized format.[19] These records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM).

Study base population. For this study, all patients with more than one prescription for either a triptan or ergotamine, alone or in combination with caffeine and cyclizine, from January 1, 1990, to December 31, 2002, were initially identified. Patients with only one prescription for a triptan or ergotamine during the study period were excluded, as this pattern of use is partially indicative of diagnostic uncertainty for migraine.[20] The date of the first presented prescription for a triptan or ergotamine during the study period was termed the start date antimigraine drug and the last ever presented prescription for one of these drugs was termed the stop date antimigraine drug.

Case and control definition. In order to investigate the association between the intensity of triptan and ergotamine use, in specific overuse and hospitalization due to ischemic complications, we performed a case-control study, nested within the study base population.

Cases were defined as all patients from the study base population who were hospitalized for the first time for a primary or secondary diagnosis that could be attributed to or exacerbated by the coronary, peripheral, or cerebral vascular side effect profile of triptans or ergotamine during the study period. These diagnoses were ischemic heart disease (ICD-9-CM codes 410, 411, and 413), Raynaud syndrome (ICD-9-CM code 443.0), unspecified peripheral vascular disease (ICD-9-CM code 443.9), vascular insufficiency of intestine (ICD-9-CM codes 557.0 and 557.9), gangrene (ICD-9-CM code 785.4), and cerebral ischemia (ICD-9-CM codes 433 to 436 and 437.0, 437.1, and 437.6). The date of hospital admission was termed the index date. Further inclusion criteria for both cases and controls were at least 1 year of observation in PHARMO before the index date, the start date antimigraine drug had to be before the index date, the stop date antimigraine drug had to be not longer ago than 1 year before the index date (current and recent use), the last dispensing date of any drug in the PHARMO database had to be after the index date, and patients had to be 18 years or older at the index date. Consequently, those patients who had their first dispensing of a specific antimigraine drug after the index date were excluded because it is not clear whether these patients already had migraine before the index date. Likewise, past users (the stop date antimigraine drug was more than 1 year before the index date) were excluded because it is not clear whether these patients still had migraine.

For each case patient, four age- ($\pm$ 5 years) and sex-matched control patients were randomly sampled from the noncases (no hospitalization due to an ischemic event during the study period) of the study base population from the same geographic area. Controls were assigned the same index date as the corresponding case. Each control could be included only once.

Exposure definition. The determinant of interest was the intensity of triptan and ergotamine use during the observation period of 1 year preceding the index date for both cases and controls. For each patient, the total consumption of these two drugs was estimated by the sum of defined daily doses (DDDs) of triptans and ergotamine dispensed in the year preceding the index date. One DDD was defined as 6 mg sumatriptan parenterally, 50 mg sumatriptan orally, 25 mg sumatriptan rectally, 20 mg sumatriptan nasally, 2.5 mg naratriptan, 2.5 mg zolmitriptan, 10 mg rizatriptan, 12.5 mg almotriptan, 40 mg eletriptan, 4 mg ergotamine single preparation by any route, and 2 mg ergotamine combination preparation by any route. Patients were subsequently categorized according to the intensity of use: 0, >0 to <30, 30 to <90, and ≥90 DDDs. Given the definition of our study base population in which we nested our case-control study, this implies that the patients assigned to the category no use (no DDDs) were not dispensed ergotamine or triptans during the year before the index date, but were dispensed antimigraine drugs before the year prior to the index date and during the years after the index date.

The revised International Classification of Headache Disorders (ICHD-II) defines medication overuse headache (MOH) for triptans and ergotamine as use on 10 or more days per month on a regular basis of at least 3 months.[21] The quantity of medicine taken per month is no longer regarded as the main criterion of overuse. From our data, we were not able to calculate the number of days on which antimigraine drugs were used. Therefore, we defined overuse as use of ≥90 DDDs during 1 year.

Potential confounding factors. In order to adjust for factors that may confound the association between antimigraine drug use and the occurrence of ischemic complications, the following covariates were studied as potential confounders: prior hospitalization 1 year prior to the index date and comedication use 1 year prior to the index date (benzodiazepines, antidepressants, antidiabetics, gastrointestinal drugs [proton pump inhibitors, H_2-antagonists], migraine prophylaxis [propranolol, atenolol, metoprolol, valproic acid, clonidine, methysergide, pizotifen, flunarizine], NSAIDs, and hormones [oral contraceptives and hormone replacement therapy]).

Data analysis. For both cases and controls, the prevalence of each characteristic during the period 1 year prior to the index date was determined. Differences between cases and controls were examined using the χ^2 test for categorical variables and independent-sample t test for continuous variables. Conditional logistic regression was used to estimate the strength of the association between the intensity of use of triptans and ergotamine and ischemic complications requiring hospitalization, expressed as crude and adjusted odds ratios (ORs) with 95% CI. The overall logistic regression model included all univariately associated (at $p < 0.1$) risk factors for ischemic complications requiring hospitalization. Stratified analysis was used to estimate the risk both of patients with and without concomitant cardiovascular drug use. Cardiovascular drug use was defined as use of one or more of the following drugs during 1 year prior to the index date: angiotensin-converting enzyme inhibitors, beta-blockers (except propranolol, atenolol, and metoprolol), calcium antagonists, diuretics, nitrates, digoxin, vitamin K antagonists, antiplatelet therapy, and lipid-lowering therapy.

In order to distinguish the outcome with individual drugs, the analysis was also performed separately for triptans and ergotamine. In this analysis, the matching factors age and gender were added to the multivariate logistic regression model.

Microsoft Access, a relational database software package, was used for database management and internal quality procedures. All statistical analyses were performed with SPSS statistical software (version 11.5).

Results. A total of 29,672 patients had commenced a triptan or ergotamine during the study period 1990 to 2002, of whom 17,439 (59%) had presented more than one

Table 1 *Baseline characteristics of cases (ischemic event) and controls (no ischemic event)*

Characteristics	Cases (n = 188), no. (%)	Controls (n = 689), no. (%)	*p* Value*
Gender			0.45
Female	127 (67.6)	485 (70.4)	
Male	61 (32.4)	204 (29.6)	
Age, y, mean (SD)	56.7 (11.8)	56.0 (11.3)	0.45
18–40	12 (6.4)	52 (7.5)	
>40–65	136 (72.3)	505 (73.3)	
>65	40 (21.3)	132 (19.2)	
Antimigraine drug			
Triptan	74 (39.3)	285 (41.3)	
Ergotamine	78 (41.5)	256 (37.2)	0.68
Both	5 (2.7)	26 (3.8)	
No use	31 (16.5)	122 (17.7)	
Prescriber			
General practitioner	153 (81.4)	525 (76.2)	
Neurologist	3 (1.6)	20 (2.9)	0.22
Other	1 (0.5)	13 (1.9)	
Unknown	0 (0)	9 (1.3)	
No use	31 (16.5)	122 (17.7)	
Mean duration (SD) to index date, y	4.36 (3.14)	4.19 (2.95)	0.49
Prior hospitalization	40 (21.3)	85 (12.3)	<0.01
Comedication			
Antidepressants	23 (12.2)	77 (11.2)	0.69
Benzodiazepines	90 (47.9)	236 (34.3)	<0.01
Cardiovascular	77 (41.0)	152 (22.1)	<0.01
Antidiabetics	7 (3.7)	11 (1.6)	0.07
Gastrointestinal	50 (26.6)	78 (11.3)	<0.01
Migraine prophylaxis	59 (31.4)	144 (20.9)	<0.01
NSAIDs	100 (53.2)	291 (42.2)	<0.01
Oral contraceptives	17 (9.0)	72 (10.4)	0.57
HRT	16 (8.5)	63 (9.1)	0.79

* χ^2 ($p < 0.1$) for comparison of proportions and independent samples *t* test ($p < 0.1$) for comparisons of means between cases and controls.

NSAIDs = nonsteroidal anti-inflammatory drugs; HRT = hormone replacement therapy.

prescription. Overall, 446 (2.6%) patients had experienced 697 hospitalizations with a primary or secondary diagnosis representing ischemic events. Patients with less than 1 year of medication history (n = 39), patients who had their first dispensing of a specific antimigraine drug after the index date (n = 54), and past users (last dispensing date of an antimigraine drug was more than 1 year before the index date; n = 157) were excluded. Further inclusion criteria resulted in a final case population compromising 188 patients. A total of 689 controls could be identified. Characteristics of the study population at the index date are described in table 1. Table 2 gives further specification of the ischemic events. Most of the events were of cardiovascular nature: 66.0% (124/188) of the whole study population, 62.2% (46/74) of the triptan users, and 71.8% (56/78) of the ergotamine users. Cerebrovascular events occurred in 26.6% (50/188) of the whole study population, in 33.8% (25/74) of the triptan users, and in 23.1% (18/78) of the ergotamine users.

Considering the whole study population, overuse of antimigraine drugs, defined as use of ≥90 DDDs in 1 year, did not increase the risk of hospitalization due to ischemic events (table 3). Stratified results according to cardiovascular drug use showed that patients using cardiovascular drugs, but not using antimigraine drugs in the year prior to the index date, had a (nonsignificant) two times higher risk of these events (OR 1.99; 95% CI: 0.83 to 4.76). Overuse of antimigraine drugs in those patients simultaneously using of cardiovascular drugs more than doubled this risk of ischemic complications (OR 4.36; 95% CI: 1.78 to 10.7).

Stratified analysis according to triptan and ergotamine use (tables 4 and 5) showed that this increased risk in patients with overuse of antimigraine drugs and use of cardiovascular drugs was clarified by overuse of ergotamine and not triptans. Considering all triptan users (table 4), triptan overuse did not increase the risk of ischemic complications (OR 0.96; 95% CI: 0.49 to 1.90). Stratified results showed that patients using cardiovascular drugs, but not using triptans in the year prior to the index date, had an almost (nonsignificant) two times higher risk of these events vs patients not using cardiovascular drugs

Table 2 *Characteristics of ischemic events of the cases*

Diagnosis	No. (N = 188)	Triptan use (n = 74)	Ergotamine use (n = 78)	Ergotamine and triptan use (n = 5)	No use (n = 31)
Cerebrovascular	50	25	18	1	6
Occlusion and stenosis of precerebral arteries	1	0	0	0	1
Occlusion of cerebral arteries	11	7	4	0	0
Transient cerebral ischemia	22	7	10	0	5
Acute, but ill-defined, cerebrovascular disease	12	8	3	1	0
Cerebral atherosclerosis	1	1	0	0	0
Other generalized ischemic cerebrovascular disease	3	2	1	0	0
Cardiovascular	124	46	56	3	19
Acute myocardial infarction	43	17	16	1	9
Other acute and subacute forms of ischemic heart disease	26	10	13	0	3
Angina pectoris	55	19	27	2	7
Peripheral	14	3	4	1	6
Peripheral vascular disease, unspecified	10	2	2	1	5
Acute vascular insufficiency of intestine	1	1	0	0	0
Gangrene	3	0	2	0	1

Table 3 *Association between intensity of antimigraine drug use and the risk of hospitalization due to ischemic events: DDDs of triptans and ergotamine dispensed during 1 year prior to the index date*

Intensity of use (DDDs)	Cases (N = 188), no. (%)	Controls (N = 689), no. (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Whole population				
0	31 (16.5)	122 (17.7)	1.0 (reference)	1.0 (reference)
>0 to <30	75 (39.9)	295 (42.8)	1.00 (0.63–1.60)	0.92 (0.57–1.50)
30 to <90	43 (22.9)	170 (24.7)	1.00 (0.59–1.67)	0.88 (0.51–1.50)
≥90	39 (20.7)	102 (14.8)	1.51 (0.88–2.58)	1.43 (0.82–2.49)
Without cardiovascular drug use				
0	19 (10.1)	94 (13.6)	1.0 (reference)	1.0 (reference)
>0 to <30	45 (23.9)	227 (32.9)	0.98 (0.55–1.77)	0.93 (0.51–1.70)
30 to <90	25 (13.3)	130 (18.9)	0.95 (0.50–1.83)	0.94 (0.48–1.83)
≥90	22 (11.7)	86 (12.5)	1.27 (0.64–2.50)	1.28 (0.64–2.56)
With cardiovascular drug use				
0	12 (6.4)	28 (4.1)	2.12 (0.92–4.90)	1.99 (0.83–4.76)
0 to <30	30 (16.0)	68 (9.9)	2.18 (1.14–4.20)	1.86 (0.92–3.74)
30 to <90	18 (9.6)	40 (5.8)	2.23 (1.06–4.68)	1.69 (0.76–3.75)
≥90	17 (9.0)	16 (2.3)	5.26 (2.27–12.2)	4.36 (1.78–10.7)

* Adjusted for prior hospitalization and use of comedication (benzodiazepines, antidiabetics, gastrointestinal drugs, migraine prophylaxis, and nonsteroidal anti-inflammatory drugs). In the analysis stratified to cardiovascular drug use, also adjusted for age and gender.

DDDs = defined daily doses; OR = odds ratio.

and not using triptans (OR 1.94; 95% CI: 0.79 to 4.76). Overuse of triptans in patients using cardiovascular drugs did not further increase this risk (OR 2.28; 95% CI: 0.68 to 7.65).

Considering all ergotamine users (table 5), it was shown that overuse of ergotamine is a risk factor for ischemic complications (OR 2.55; 95% CI: 1.22 to 5.36). Overuse of ergotamine by those patients without cardiovascular drug use slightly increased the risk of ischemic complications without reaching significance (OR 2.19; 95% CI: 0.84 to 5.68). Patients using cardiovascular drugs during the year prior to the index date, but not using ergotamine, had a (nonsignificant) two times higher risk of these complications (OR 2.20; 95% CI: 0.90 to 5.36). Overuse of ergotamine in patients simultaneously using cardiovascular drugs increased this risk almost fourfold (OR 8.52; 95% CI: 2.57 to 28.2).

Discussion. Our research shows that overuse of triptans (defined as use of ≥90 DDDs per year), neither in the general population nor in those using

Table 4 *Association between intensity of triptan use and the risk of hospitalization due to ischemic events: DDDs of triptans dispensed 1 year before the index date*

	Triptan users (n = 359) and no antimigraine drug use (n = 153)			
Intensity of use (DDDs)	Cases (n = 105), no. (%)	Controls (n = 407), no. (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
All patients				
0	31 (29.5)	122 (30.0)	1.0 (reference)	1.0 (reference)
>0 to <30	36 (34.3)	137 (33.6)	1.03 (0.60–1.77)	0.86 (0.49–1.53)
30 to <90	19 (18.1)	81 (19.9)	0.92 (0.49–1.74)	0.78 (0.40–1.53)
≥90	19 (18.1)	67 (16.5)	1.12 (0.59–2.13)	0.96 (0.49–1.90)
Without cardiovascular drug use				
0	19 (18.1)	94 (23.1)	1.0 (reference)	1.0 (reference)
>0 to <30	28 (26.7)	103 (25.3)	1.35 (0.71–2.57)	1.17 (0.60–2.30)
30 to <90	12 (11.4)	66 (16.2)	0.90 (0.41–1.98)	0.80 (0.35–1.81)
≥90	12 (11.4)	58 (14.3)	1.02 (0.46–2.26)	0.94 (0.41–2.13)
With cardiovascular drug use				
0	12 (11.4)	28 (6.9)	2.12 (0.92–4.90)	1.94 (0.79–4.76)
>0 to <30	8 (7.6)	34 (8.3)	1.16 (0.47–2.91)	0.7 (0.28–2.04)
30 to <90	7 (6.7)	15 (3.7)	2.31 (0.83–6.43)	1.61 (0.53–4.88)
≥90	7 (6.7)	9 (2.2)	3.85 (1.28–11.6)	2.28 (0.68–7.65)

* Adjusted for age, gender, prior hospitalization, and use of comedication (benzodiazepines, antidiabetics, gastrointestinal drugs, migraine prophylaxis, and nonsteroidal anti-inflammatory drugs). Combined use of triptans and ergotamine was excluded in the analysis.

DDDs = defined daily doses; OR = odds ratio.

Table 5 *Association between intensity of ergotamine use and the risk of hospitalization due to ischemic events: DDSs of ergotamine dispensed 1 year before the index date*

Intensity of use (DDDs)	Ergotamine users (n = 334) and no antimigraine drug use (n = 153)			
	Cases (n = 109), no. (%)	Controls (n = 378), no. (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
All patients				
0	31 (28.4)	122 (32.3)	1.0 (reference)	1.0 (reference)
>0 to <30	38 (34.9)	149 (39.4)	1.00 (0.59–1.71)	1.00 (0.57–1.72)
30 to <90	21 (19.3)	78 (20.6)	1.06 (0.57–1.98)	1.01 (0.52–1.95)
≥90	19 (17.4)	29 (7.7)	2.58 (1.28–5.19)	2.55 (1.22–5.36)
Without cardiovascular drug use				
0	19 (18.1)	94 (24.9)	1.0 (reference)	1.0 (reference)
>0 to <30	17 (26.7)	116 (30.7)	0.73 (0.36–1.47)	0.77 (0.38–1.58)
30 to <90	11 (11.4)	56 (14.8)	0.97 (0.43–2.19)	1.10 (0.47–2.53)
≥90	9 (11.4)	22 (5.8)	2.02 (0.81–5.07)	2.19 (0.84–5.68)
With cardiovascular drug use				
0	12 (11.4)	28 (7.4)	2.12 (0.92–4.90)	2.20 (0.90–5.36)
>0 to <30	21 (7.6)	33 (8.7)	3.15 (1.51–6.58)	3.26 (1.45–7.36)
30 to <90	10 (6.7)	22 (5.8)	2.25 (0.92–5.51)	2.21 (0.81–6.05)
≥90	10 (6.7)	7 (1.9)	7.07 (2.39–20.9)	8.52 (2.57–28.2)

* Adjusted for age, gender, prior hospitalization, and use of comedication (benzodiazepines, antidiabetics, gastrointestinal drugs, migraine prophylaxis, and NSAIDs). Combined use of ergotamine and triptans was excluded in the analysis.

DDDs = defined daily doses; OR = odds ratio.

cardiovascular drugs, increases the risk of cerebral, cardiovascular, or peripheral ischemic complications requiring hospitalization. Ergotamine overuse in patients simultaneously using cardiovascular drugs, on the contrary, increases the risk of these ischemic complications almost fourfold vs patients using cardiovascular drug but not using ergotamine.

Our results correspond with in vitro pharmacologic data that show that, at therapeutically relevant concentrations, triptans have little potential to cause clinically relevant constriction of nondiseased coronary arteries.[22] As shown recently by in vivo data, this might also be applied to diseased coronary arteries.[23] We had too few cases on which to perform a separate analysis for cerebral, coronary, and peripheral ischemic events. Therefore, we do not know whether (over)use of triptans, being powerful vasoconstrictors of the cerebral arteries, increases the risk of ischemic stroke. However, the absolute risk of this potential adverse event of triptans remains low. Furthermore, all triptans produce substantially less potent arterial constriction than ergotamine.[22]

Two comparable studies have been published recently. The first study investigated the incidence of stroke, cardiovascular events and death in a migraine cohort, stratified by triptan prescription, and found that in general practice triptan treatment did not increase the risk for these events.[14] However, in this study, the intensity of triptan use and the differential risk of ergotamine use were not taken into account. These two aspects were (partly) studied in the second study, investigating the rates of vascular events in relation to dispensing of triptans and ergotamine among migraineurs.[16] Overall, in the group of migraineurs, neither current nor recent triptan or ergotamine use was associated with an increased risk of myocardial infarction, unstable angina, serious ventricular arrhythmia, stroke, or TIA compared with no use. Intensity of triptan and ergotamine use was only investigated in relation to the occurrence of stroke. No association was found for triptan use. Recent use of ergotamine showed an increased risk of stroke in only one category of use (11 to 28 days supplied in the past 6 months) compared with no use (OR 4.54; 95% CI: 2.26 to 9.10). In the highest category of use (ergotamine supplied ≥61 days in the past 6 months), no increased risk of stroke was found. No distinction was made of whether cardiovascular drugs were used.

Several limitations of our analysis should be mentioned. First, different validity studies indicate that certain conditions may not be accurately reflected by discharge ICD-9 codes. One study investigated the sensitivity and the positive predictive value (PPV) of the ICD-9 codes 434 and 436 in a general hospital in Italy.[24] They found a sensitivity of 82% and a PPV of 76%. An administrative database of five academic medical centers in the United States found a PPV of 85% for ICD-9 code 434, and 77% for the ICD-9 codes 435 and 436.[25] Dutch validity studies for the ICD-9 discharge codes that we used have not been published so far. However, a low sensitivity rate means that among controls one could find some cases (false negatives), which would have diluted our results. A low PPV means that not all our cases truly are cases (false positives). Because there is no reason to assume that these false positive cases would have used more antimigraine drugs, this would not have overpowered, but probably rather diluted, our estimates.

Second, the duration of exposure had to be esti-

mated because the PHARMO database contains only data about the dates and quantities of drug dispensing and not information about the actual moments of drug intake by the patient. However, estimation of drug overuse not need be a problem because prescriptions repeated consistently can serve as strong evidence of drug use by patients.[26] We admit that our cutoff of ≥90 DDDs per year is somewhat arbitrary. Therefore, we performed an additional analysis in which we divided the last category (≥90 DDDs) into two categories: 90 to <150 DDDs and ≥150 DDDs. The observed pattern (increasing risk of ischemic complications with increasing dispensing of ergotamine, but not triptans) was comparable with the pattern using a cutoff of ≥90 DDDs (data not shown). However, the extra category meant loss of power because only a few patients were in these last two categories (90 to <150 DDDs and ≥150 DDDs). Therefore, we chose not to split the category ≥90 DDDs and defined this last category as overuse.

Furthermore, a recent meta-analysis showed the association between migraine and ischemic stroke.[27] Therefore, it is possible that an increased intensity in use reflects an increased severity of migraine, being the actual cause of the ischemic stroke. However, in this case, one would expect that for both triptans and ergotamine, a higher percentage of overuse in the case group compared with the control group. Triptan overuse was about equal in both cases and controls.

Although adjusted for potential confounders, residual confounding may exist because a few factors known to be associated with increased risk of coronary and cerebrovascular complications such as smoking, family history, obesity, and fitness were unknown. Despite these limitations, we believe that our research contributes to the confirmation of the safety of triptans and emphasizes the risk of ischemic complications due to ergotamine overuse, so far only described in case reports.

We also determined whether increasing use of triptans and ergotamine shortly before the index date was associated with the risk of hospitalization. Therefore, we computed the distribution of the total number of DDDs dispensed across the year preceding the index date in monthly intervals for each eligible patient, expressed as the pattern score. This method was adapted from a study that investigated the intensity of β-agonist inhaler therapy.[28] The pattern score may range from 1 to 12. The score 1 indicates that the total DDDs were dispensed during the first monthly interval and none in the remaining intervals and the score 12 indicates that all DDDs were concentrated in the 12th month interval and none in the previous intervals. Contrary to our expectations, the pattern score (expressed as categorized pattern scores: 0, >0 to ≤5, >5 to <7, ≥7) did not differ significant between the cases and controls. Based on the pharmacologic properties of triptans and ergotamine, we expected that increased use of these drugs shortly before the ischemic event would be a risk factor for the occurrence of this event. Apparently it was not.

Due to their vasoconstrictive pharmacodynamic properties, triptans and ergotamine are contraindicated in patients with cardiovascular risk factors. Therefore, as one would expect, it was previously found that triptans were prescribed to those at less risk of cardiovascular events.[14] Remarkably, in our population, we found that the percentage of patients who did not use specific antimigraine drugs during the study period was 17.5% (40/229) in those using cardiovascular drugs vs 17.4% (113/648) in those not using cardiovascular drugs. Also patients who used cardiovascular drugs were dispensed as much specific antimigraine drugs as patients who did not use cardiovascular drugs (mean DDDs per year [excluding no use]: 56.0 vs 56.2). It has to be noted that we did not categorize the number of different cardiovascular drugs used, and therefore no distinction was made between patients at high and patients at low cardiovascular risk. This might probably explain part of the finding that patients using cardiovascular drugs (but not using antimigraine drugs) showed only a nonsignificant two times higher risk of ischemic complications vs patients not using cardiovascular drugs (and not using antimigraine drug). Furthermore, we found that more than 60% (114/188) of the cases were still dispensed a specific antimigraine drug after their ischemic event. Notably, this did not result in a higher risk of a second ischemic event: 28.1% (32/114) of those who continued to use triptans or ergotamine had a second event compared with 29.7% (22/74) of those who discontinued use. A possible explanation for these striking results could be that antimigraine drugs were in particular discontinued in those who were at high risk of another event.

Interactions between ergotamine and comedication may predispose to ergot toxicity. One of the most reported interactions with ergotamine is coadministration with the macrolide antibiotics erythromycin and clarithromycin, causing increased bioavailability due to inhibition of cytochrome P-450 3A4.[29-32] Protease inhibitors may also interact with ergotamine.[33-35] Only six of our cases used ergotamine in combination with erythromycin or clarithromycin during the period 1 year before the index date. In all cases, the dispensing date was ≥1 month prior to the index date (1, 2, 3, 5, 10, and 11 months) and therefore less likely related to the ischemic event. Protease inhibitors were not used by our study population during 1 year prior to the index date. Because also other drugs (strongly) inhibit CYP3A4, these drugs may also have interfered with ergotamine. We did not study all these possible interfering drugs. However, if these kinds of drug interactions played a role in our data, it would have diluted our results.

Overall, we provided evidence that, regarding the occurrence of ischemic complications requiring hospitalization, triptan use and even triptan overuse are safe in general practice. Possibly due to its stronger

vasoconstrictive properties, overuse of ergotamine may increase the risk of these complications, especially in those simultaneously using cardiovascular drugs. Moreover, because we did not distinguish between patients with low and patients with high cardiovascular risk, we did not investigate the attributable risk of specific antimigraine drugs to the occurrence of ischemic complications in specific populations as those with a high cardiovascular risk profile. Therefore, this conclusion cannot be extended to such a population, and when prescribing specific antimigraine drugs to these patients, one still should take the contraindications into account.

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