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Post-Marketing Surveillance of Ischaemic Optic Neuropathy in Male Veterans Co-Prescribed Phosphodiesterase-5 Inhibitors with Organic Nitrates or α-Blockers

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Abstract

Background: The cause of nonarteritic anterior ischaemic optic neuropathy (ION) is unknown, although assumed to be related to transient vascular insufficiency of the optic nerve head. Because the interaction of phosphodiesterase-5 (PDE-5) inhibitors with either an organic nitrate or α-blocker may theoretically increase the risk of ION, we conducted a screening study to determine if such a risk might exist.

Methods: Retrospective cohort study of male veterans with ION and possible ION. The national Veterans Health Administration (VHA) clinical database was cross-referenced (linked) with the VHA pharmacy database looking for specific drug combinations.

Results: Compared with no use, the relative risk (RR) of ION and possible ION for men prescribed both PDE-5 inhibitor and organic nitrate was 1.41 (95% CI 0.85, 2.33). Similarly, the RR of ION and possible ION with concurrent prescription of PDE-5 inhibitor and α-blocker was 1.21 (95% CI 1.01, 1.44). When risk was measured against use of a PDE-5 inhibitor alone, the RR was 1.29 (95% CI 0.78, 2.16) for PDE-5 inhibitor and organic nitrate and 1.12 (95% CI 0.92, 1.35) for PDE-5 inhibitor and α-blocker.

Conclusions: We linked two large national databases to screen for a potentially important drug-drug-disease interaction. There was no increase in risk of ION and possible ION in men dispensed a PDE-5 inhibitor with either organic nitrates or an α-blocker compared with men dispensed PDE-5 inhibitor alone. An incidental observation that a substantial number of men were prescribed both an organic nitrate and a PDE-5 inhibitor within a single dispensing period raises concerns over non-ocular safety issues. The wisdom of co-dispensing medications that are contraindicated may deserve a broader audience.

Nonarteritic anterior ischaemic optic neuropathy (ION) is characterized by sudden and painless loss of vision in the eye, usually with optic disc oedema, in the absence of arteritis. Case reports of nonarteritic anterior ION occurring from 30 minutes to 36 hours after the use of a phosphodiesterase-5 (PDE-5) inhibitor suggest a possible causative association.[1-9] Because men who use PDE-5 inhibitors for erectile dysfunction tend to have a similar clinical profile to men who develop nonarteritic anterior ION (e.g. older age and general vasculopathic risk factors), the relationship could be nothing more than coincidental. Although the known effects of PDE-5 inhibitors on the cardiovascular system make the potential association of ischaemic optic nerve disease biologically plausible, there is no conclusive evidence to support a causal relationship.

In a recent retrospective investigation to determine the feasibility of a case-control study, we found that the use of PDE-5 inhibitors in male veterans ≥50 years of age (n = 479 489) was associated with a marginal increased risk of ION and 'possible' ION (papillitis and optic neuritis) [relative risk {RR} = 1.10; 95% CI 1.02, 1.20].[10] The majority of all prescriptions for PDE-5 inhibitors were for sildenafil 100 mg (99.4%). Because this was a retrospective study, no causal inference could be drawn. Although the findings were consistent with anecdotal reports linking the disorder with PDE-5 inhibitor use, the risk, if real, is low enough to be masked by how closely the drug effect competes with other risk factors to explain the disease outcome.[11,12]

Although several types of acute events have been associated with nonarteritic anterior ION (e.g. cataract extraction, surgical hypotension, acute blood loss), major risk factors for nonarteritic anterior ION include hypertension (treated or untreated), sleep apnoea, tobacco use, diabetes mellitus and small cup-to-disc ratio.[13-17] Although heart disease, angina and thromboembolic disease are prevalent among patients with nonarteritic anterior ION, they do not appear to be associated independently with the clinical disease.[13-17]

During the course of our investigation into the feasibility of a case-control study, which spanned the 2 fiscal years (FYs) 2004 and 2005, we were struck by what appeared to be a substantial number of prescriptions for PDE-5 inhibitors issued to men prescribed organic nitrates. The use of a PDE-5 inhibitor and systemic organic nitrate is generally regarded as 'contraindicated' because of the potential for the two medications to cause an unsafe decrease in blood pressure.[18] We wondered if the use of an organic nitrate might confer an increased risk of nonarteritic anterior ION in men taking a PDE-5 inhibitor. A similar question as to the interactive effects of α-blockers on optic nerve perfusion was raised because of the effects on blood pressure.[19] To investigate this question further, we cross-referenced, or linked, a 2-year national cohort of male veterans diagnosed with ION, papillitis and optic neuritis, with the national Veterans Health Administration (VHA) pharmacy database looking for any possible association.

Material and Methods

Sources of Data

Two national VHA datasets were used to obtain information on drug utilization and medical diagnoses for FYs 2004 and 2005 (1 October 2003 through 30 September 2005). The number of unique users of PDE-5 inhibitors (sildenafil, tadalafil and vardenafil) was identified through the VHA Decision Support Systems (DSS) national pharmacy extracts. The pharmacy extract included patient age, number of prescriptions and the number of pills or tablets dispensed. The VHA National Patient Care Database was used to identify men ≥50 years of age that were newly diagnosed with ION and other optic neuropathies that could be confused with nonarteritic anterior ION during the same FYs.

Identifying Patient Cohort

The International Classification of Diseases (9th ed.), Clinical Modification (ICD-9-CM), was used to identify study cases of ION (ICD-9-CM 377.41). The ICD-9-CM nomenclature does not distinguish

anterior ION as a distinct entity from ION, nor does it have a distinct code for nonarteritic disease. For the purpose of this study, the definition of nonarteritic anterior ION was based on the diagnosis of ION (ICD-9-CM 377.41) in the absence of diagnoses for temporal arteritis (ICD-9-CM 446.5) or polymyalgia rheumatica (ICD-9-CM 725). Given the inherent clinical difficulty in diagnosing the optic neuropathies (particularly the clinical overlap of ION and demyelinating disease[13]), a second study group of 'possible' ION was created using the following codes: 'optic neuritis, other' (ICD-9-CM 377.39), 'optic neuritis, unspecified' (ICD-9-CM 377.30) and 'optic papillitis' (ICD-9-CM 377.31). Male veterans with previous or concurrent diagnoses of temporal arteritis (ICD-9-CM 446.5) or polymyalgia rheumatica (ICD-9-CM 725) were excluded from the study.

To reduce the chances that a previous optic neuropathy might be confused with ION, veterans with an historical diagnosis of optic nerve disease (e.g. optic atrophy, nutritional optic neuropathy, ION) were removed from the database according to ICD-9-CM codes 377.00 through 377.9 for the two previous FYs before performing the disease-specific searches.

Identification of Medication Dispensed

The national pharmacy extracts were used to identify male veterans aged ≥50 years who received at least one prescription for a PDE-5 inhibitor during the FYs 2004 through 2005. These men were then cross-referenced (or linked via a scrambled patient identifier) to the clinical datasets within the ION and possible ION study groups compiled from the National Patient Care Database.

We performed a similar data search (FYs 2004 and 2005) for concomitant dispensing of systemic organic nitrates and α-blockers. To increase the likelihood that a PDE-5 inhibitor and organic nitrate or α-blocker were taken in proximity to one another, the prescription refill dates were temporally aligned to overlapping dates. In calendar time, this overlap corresponds to a 30-day interval, or one refill date.

Logistic regression models included patient age, diagnosis of diabetes (ICD-9-CM codes: 250, 250.0–250.9), diagnosis of hypertension (ICD-9-CM codes: 401–405), diagnosis of sleep apnoea (ICD-9-CM codes: 327.20, 327.21, 327.23, 327.24, 327.26, 327.27, 780.51, 780.53, 780.57) and tobacco use (ICD-9-CM code: V15.82).[13-17] The models examine the odds of ION for co-prescribed medications to PDE-5 inhibitor alone. Small optic nerve cup-to-disc ratio could not be included in the models because optic disc morphology is not recorded in the medical database.

Statistical calculations were carried out using SAS software (SAS Institute, Cary, NC, USA). RRs were calculated as the ratio of incidence of ION among men exposed to the selected drugs to the incidence of ION among men not exposed. The study protocol was approved through the University of South Florida Institutional Review Board and the James A. Haley Research and Development Committee for compliance with human subject protection.

Results

There were 4 157 357 male veterans aged ≥50 years in the VHA for FYs 2004 through 2005, following the exclusion of men with a previous diagnosis of optic nerve disease, temporal arteritis or polymyalgia rheumatica. During the 2 study years, there were 3777 unique entries for ION and 1530 unique entries for possible ION.

Over the 24-month study, 479 489 unique male veterans aged ≥50 years were dispensed a PDE-5 inhibitor (11.5% of eligible veterans). The national pharmacy database for FYs 2004 and 2005 revealed 24 606 or 5.1% (24 606/479 489) individual male patients aged ≥50 years who received both a PDE-5 inhibitor and an organic nitrate (21% cutaneous patches, 42% sublingual, 36% oral and ~1% spray). The number of patients who received both medications within a single refill interval (typically 30 days) was 8344 (or 1.7% of men prescribed a PDE-5 inhibitor aged ≥50 years). During the same 2-year period, 97 972 or 20.4% (97 972/479 489) men aged ≥50 years were prescribed both a PDE-5 inhibitor

Table I. Baseline characteristics of patients by group

Characteristic	PDE-5 alone	PDE-5 and nitrates	PDE-5 and α-blockers
Mean age	64	67	68
Proportion with diabetes mellitus	0.40	0.38	0.41
Proportion with hypertension	0.58	0.77	0.67
Proportion with sleep apnoea	0.01	0.00	0.01
Proportion using tobacco	0.02	0.00	0.01

PDE-5 = phosphodiesterase-5.

and systemic α-blocker. When temporally aligned to a refill interval, the number was 84 169 (or 17.6% of men prescribed a PDE-5 inhibitor aged ≥50 years).

Fifteen patients with ION or possible ION had been dispensed a PDE-5 inhibitor and organic nitrate within a single refill interval (2.2% of 670 study patients with ION/possible ION who had been prescribed a PDE-5 inhibitor). The RR of ION/possible ION for men prescribed both drugs was 1.41 (95% CI 0.85, 2.33). One hundred and twenty-nine men with ION or possible ION were dispensed a PDE-5 inhibitor and systemic α-blocker (19.3% of 670 study patients with ION/possible ION with PDE-5 inhibitor). The RR of ION/possible ION was 1.21 (95% CI 1.01, 1.44). Results did not vary for either drug combination when examined by subgroups of ION and possible ION.

When the risk of ION and possible ION for men who were dispensed drug combinations was compared with that risk in men dispensed a PDE-5 inhibitor alone, the RR for the PDE-5 inhibitor and organic nitrate group was 1.29 (95% CI 0.78, 2.16), and 1.12 (95% CI 0.92, 1.35) for the PDE-5 inhibitor and α-blocker group.

No statistically significant changes in risk were identified when adjusted for age, hypertension, tobacco use and sleep apnoea using logistic regression models (see table I and table II).

Discussion

This study used a large-scale surveillance technique to screen for rare but potentially important drug-related adverse effects. It takes advantage of two enormous databases, which link clinical outcomes with drug utilization. The number of patients in the national veteran population who are exposed to new commercial drugs each year is usually sufficiently large to reveal complications that could have been missed during pre-market drug testing. Although there are several important limitations of using retrospective data for drug safety surveillance, the purpose of this study was to identify safety issues and not to establish definitive risk ratios.

The VHA DDS database captures ambulatory encounters at outpatient clinics throughout the US. The database includes fields for diagnosis, procedures and type of clinic visit, to name just a few. The pharmacy database includes information related to prescription type, unit dose and the number of days supplied. The information is encrypted and, for the purposes of our research, de-identified. We could not examine patient medical records to validate a causal association between drug use and ION because those records were protected health information under the Health Insurance Portability and Accountability Act (HIPAA). As an alternative, we examined the DSS National Patient Care database for co-morbidities through ICD-9-CM codes, which

Table II. Odds ratio of ischaemic optic neuropathy co-prescribed medication to a phosphodiesterase-5 (PDE-5) inhibitor alone

Characteristic	PDE-5 and nitrates [odds ratio (95% CI)]	PDE-5 and α-blockers [odds ratio (95% CI)]
Age	1.03 (1.00, 1.08)	1.06 (1.03, 1.08)
Diabetes mellitus	1.15 (0.35, 3.74)	1.20 (0.78, 1.87)
Hypertension	2.21 (0.57, 8.60)	1.43 (0.91, 2.25)
Sleep apnoea	<0.01 (0.005, >9)	1.74 (0.19, 16.08)
Tobacco use	<0.01 (0.005, >9)	0.35 (0.04, 2.79)

maintained HIPAA compliance. Documentation and manuals of the databases are available online from the Veterans Information Resource Center (http://www.virec.research.va.gov/).

Among the major limitations of using large medical databases for surveillance studies is the inability to verify the accuracy of individual entries and the lack of uniform training for persons making entries. The VHA also has its own unique properties, being an institution serving mostly men. Veterans are free to obtain care on the outside, which might bias patient enrolment towards men in lower socioeconomic groups or men without medical insurance. However, despite these limitations, the magnitude of the database (>4 million men ≥50 years of age) makes it ideal for screening for uncommon or rare drug complications. Another limitation of post-marketing surveillance studies is the inability to verify if patients actually took the medications they were prescribed.

In an earlier study of ION and the use of PDE-5 inhibitors, we found a marginal increase in the unadjusted risk of all types of optic neuropathy (but not the ischaemic subtype) associated with dispensing of these medications (RR = 1.10; 95% CI 1.02, 1.20).[10] The small magnitude of this risk provided useful information for planning a case-control study to help resolve the issue of causality. When collecting data for this study, we were struck by the number of men prescribed both organic nitrates and PDE-5 inhibitors.

In the current study, we found a marginal increase in the risk of ION and possible ION associated with concurrent dispensing of PDE-5 inhibitors and α-blockers, but no increased risk with concurrent dispensing of PDE-5 inhibitors and organic nitrates. Neither of these risks was significantly different from that associated with the use of a PDE-5 inhibitor alone. These findings are reassuring in the sense that they do not reveal any trend for substantive risk of ION despite a biologically plausible mechanism for additive injury.

One of the difficulties in assessing the risk of ION with the use of drugs such as PDE-5 inhibitors, or certain drug combinations, is that the proposed mechanism of drug injury (i.e. hypoperfusion of the optic nerve head) is essentially the same as the proposed disease mechanism itself.[14-17] Men who are prescribed PDE-5 inhibitors, organic nitrates or α-blockers usually share one or more of the common vasculopathic risk factors for ION.[14,17] Men with diabetes and high blood pressure are actually targeted (marketing and direct-to-consumer advertising) on television commercials and media advertisements by manufacturers of PDE-5 inhibitors. Any small additive risk of ION (which is a relatively uncommon condition in the general population) conferred by a widely prescribed drug might easily go unnoticed among a population of men who already have or are predisposed to small-vessel disease.

Although there appears to be no increased risk of ION/possible ION in men dispensed a PDE-5 inhibitor and an organic nitrate, the fact that many men received both prescriptions in close proximity to one another raises concerns about other non-ocular health outcome issues not studied here. This concern extends to a larger group of men prescribed an organic nitrate and a PDE-5 inhibitor who are at risk of stroke, fall-related injury or myocardial ischaemia should their blood pressure fall precipitously from a drug-drug interaction.

Pharmacological studies have shown that the concurrent use of a PDE-5 inhibitor and a systemic α-blocker has minimal effects on blood pressure and pulse;[18,19] however, the interaction of PDE-5 inhibitors and organic nitrates are haemodynamically significant and possibly dangerous.[20] The 1.7% of men aged ≥50 years who were prescribed a PDE-5 inhibitor and organic nitrate within a single dispensing period may not seem that alarming; however, it translates to >8000 individual patients within the VHA. How this proportion compares with private and non-government healthcare systems in the US and other countries is unknown since data on the subject are not available for comparison. Then again, the actual number of men taking both medications in close proximity to one another could be considerably greater, since 5.1% of men aged ≥50 years who had been prescribed a PDE-5 inhibitor

had a prescription for an organic nitrate over the 2-year study period (24 606 individuals). Since PDE-5 inhibitors and organic nitrates are usually used on an 'as needed' basis, patients probably take these prescriptions well beyond a single prescribing interval. The critical question brought up by the observation of concurrent yet contraindicated prescriptions is whether being prescribed medications in this manner increases the likelihood that they might be taken in close proximity to one another or increase the risk of other potential adverse events. One study found that the use of PDE-5 inhibitors did not increase the overall risk of acute myocardial infarctions;[21] however, the population-based effects of the interaction of PDE-5 inhibitors and organic nitrates have yet to be determined. Theoretically, men taking both drugs in close proximity to one another could experience a clinically significant fall in myocardial or cerebral perfusion, leading to acute coronary syndrome, stroke or a fall-related injury.

On 22 September 2006, the Institute of Medicine released its findings for drug safety in the US, noting the need for administrative data to improve the drug safety and postmarketing surveillance capabilities in the US.[22-24] Later, on 30 January 2007, the US FDA and the VHA announced that they had signed a memorandum of understanding to share information and expertize related to the review and use of FDA-regulated drugs, biologics and medical devices (medical products) to enhance post-marketing medical product safety data collection and improve risk communication through more robust interagency activities.[25] These US initiatives reflect efforts to move from a reactive to a more proactive pharmacovigilance system that may ultimately be part of a larger and evolving worldwide drug safety system as conceptualized in the Erice Manifesto 2007.[26] Our study demonstrates the usefulness of large-scale national databases to identify a susceptible cohort for surveillance purposes.

Conclusions

We linked two large national databases to screen for a potentially important drug-drug-disease interaction. The marginal increase risk of ION and possible ION in men receiving a PDE-5 inhibitor who were prescribed an α-blocker was no different from that for men who were prescribed a PDE-5 inhibitor alone. Although there was no increased risk of ION or possible ION in men prescribed PDE-5 inhibitors and organic nitrates, the number of men prescribed both medications raises concerns about non-ocular safety issues, since these two medications are generally considered contraindicated.

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