

Hiccups in Parkinson's disease: an analysis of cases reported in the European pharmacovigilance database and a review of the literature

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Received: 31 January 2017 / Accepted: 26 May 2017 / Published online: 9 June 2017
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Abstract

Background Some reports have suggested an association between dopamine agonists and hiccups, involuntary contractions that merit full clinical attention because they can be very debilitating. Many drugs frequently used to treat hiccups are formally contraindicated in Parkinson's disease due to their liability to worsen motor symptoms, making the treatment of hiccups problematic in this disease. The objective of the present study was to analyze all spontaneous reports of hiccups from the European Pharmacovigilance Database in patients with Parkinson's disease and/or on dopaminergic drugs. Finally, we sought to identify evidence-based recommendations on the management of hiccups in Parkinson's disease. **Methods** We searched for all reports of hiccups in the European Pharmacovigilance Database (EudraVigilance) and calculated proportional reporting ratios for dopamine agonists and hiccups. We reviewed the literature on Parkinson's

disease, dopamine agonists, and hiccups, searching for specific treatment recommendations for hiccups in this disease.

Results Both rotigotine and pramipexole fulfilled the criteria to generate a safety signal. We found 32 and 13 cases of hiccups associated with dopamine agonists in EudraVigilance and the literature, respectively. There were no specific recommendations for the management of hiccups in Parkinson's disease in the clinical guidelines consulted.

Conclusions We have found evidence that rotigotine and pramipexole are associated with the appearance of hiccups and that this adverse reaction occurs predominantly in males. Given the scarce information available, specific recommendations are needed in clinical guidelines for the adequate management of hiccups in Parkinson's disease.

Keywords Adverse drug reaction · Hiccups · Parkinson's disease (PD) · Dopamine agonist · Pharmacovigilance

Electronic supplementary material The online version of this article (doi:10.1007/s00228-017-2275-6) contains supplementary material, which is available to authorized users.

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Introduction

Hiccups are sudden, involuntary, spasmodic contractions of the diaphragm and external intercostal muscles that result in inspiration, which abruptly end with the closure of the glottis. Although little is known about the pathophysiological mechanisms underlying hiccups, it has been found that the causes are heterogeneous, both peripheral and central factors contributing to their induction [1].

Some reports have suggested an association between dopamine agonists and hiccups, although the information is scarce [2–8]. Interestingly, a study carried out in Japan including 90 patients with Parkinson's disease (PD) showed that hiccups were more prevalent in individuals with the disease than in healthy volunteers (20% in PD versus 3%). The authors suggested that not only pharmacological (extrinsic) but also

intrinsic factors may be associated with hiccups in PD, since some of the patients reported suffering from hiccups before starting antiparkinsonian treatment [1]. Other authors have stated that hiccups might represent an overlooked non-motor symptom of the disease [9, 10]. One hypothesis is that dopamine receptors could be involved in generating hiccups. In this context, some authors have described that a relationship between dopamine agents and D₃ dopamine receptor plays a role in the generation of hiccups [7].

Although hiccups have often been regarded as a negligible symptom in clinical practice, they merit full clinical attention because they can be very debilitating. Indeed, intractable hiccups can be associated with potentially fatal consequences, and safe management may be challenging [7]. Numerous agents have been tried for the treatment of hiccups. In a 2015 systematic review of pharmacological treatments for persistent/intractable hiccups, Steger et al. noted that treatment of the underlying condition was the most successful approach, but there were no high-quality data on which to base specific recommendations on pharmacologic treatment [11]. However, considering the limited data available, the researchers indicated that baclofen and gabapentin should be considered the first-line therapy for persistent/intractable hiccups, owing to their lower risk of adverse effects, keeping metoclopramide and chlorpromazine in reserve. Given the aforementioned conclusions, the treatment of hiccups in PD patients may be problematic, because many of these frequently used drugs are contraindicated in Parkinson's disease, given their liability to worsen motor symptoms [12].

Considering the scarce knowledge about the management of hiccups in PD patients, the objective of the present study was to gain deeper insight into the problem of hiccups in this population. First of all, we analyzed all the spontaneous reports of hiccups from the European Pharmacovigilance Database (EudraVigilance) in patients with PD and/or undergoing treatment with dopaminergic drugs. Secondly, we reviewed all the available literature focusing on cases of hiccups associated with dopaminergic agents and/or PD. Finally, we sought in the main guidelines to identify evidence-based recommendations on the management of hiccups in PD.

Methods

Hiccups as an adverse drug reaction in the European pharmacovigilance database (EudraVigilance)

Firstly, we searched all reports of hiccups recorded in the European Pharmacovigilance Database (EudraVigilance). EudraVigilance is the centralized European database of suspected adverse reactions to medicinal products that are authorized or being studied in clinical trials in the

European Economic Area (EEA). This database receives data from case reports filed by the national drug regulatory agencies and pharmaceutical companies. Suspected adverse reactions are recorded in EudraVigilance according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

We searched for all cases of hiccups (this being the preferred term in MEDDRA, version 17.1) from 1st January 2001 to 15th May 2016. Later, we selected cases of hiccups associated with any dopamine agonist (N04B ATC code group) and also any occurring in PD patients, these cases being detected by analyzing the structured medical history records in EudraVigilance. Patients under 18 years old were excluded from the analysis. Data on country, sex, age, severity, causality, and drug involved were analyzed for each patient. Causality assessment was performed with the official method of the Spanish Pharmacovigilance System, which is based on the modified Karch-Lasagna probability scale [13]. Each case was classified into one of the following categories: probable, possible, or doubtful. Severity assessment was performed according to the European Union (EU) criteria. Specifically, the EU Codification Directive (directive 2001/83/EEC) defines a serious reaction as an adverse reaction that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Secondly, a case/non-case analysis was performed to evaluate the association between exposure to dopamine agonists and hiccups by calculating the proportional reporting ratios (PRRs) for dopamine agonists and hiccups. This involves calculation of a specified reaction, in this case hiccups, for drugs of interest, in our study dopamine agonists, where the comparator is all other drugs in the database as a measure of disproportionality. The expected or null value for a PRR is 1, and values generated are a measure of strength of association, behaving in a similar way to relative risks. Measures of statistical association may be calculated using a confidence interval around the PRR [14]. In EudraVigilance, to generate a safety signal, which is information on a new or known adverse event that is potentially caused by a drug, the lower bound of the 95% CI of the PRR is required to be ≥ 1 and the number of individual cases to be ≥ 3 . All calculations were performed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY).

Review of the literature

We performed a review of the literature on PD, dopamine agonists, and hiccups. A systematic search of MEDLINE was conducted in May 2016 with the following PubMed query MeSH terms: “Parkinson disease” AND “hiccups” OR “dopamine agonists” AND “hiccups” with no language

restrictions. We also retrieved additional publications from the reference list of the selected articles. All selected studies retrieved in the MEDLINE search were used as a starting point for the “related citation” strategy of PubMed. Moreover, we used Google Scholar to perform a citation analysis of the selected studies, with a check of the content of the relevant retrieved citations. We excluded studies that did not refer to hiccups associated with dopaminergic drugs. A flowchart of the search strategy can be consulted as supplementary data, Fig. 1.

Review of hiccups treatment and management in PD

We searched for the following terms: “hiccups,” “hiccup,” “hiccoughs,” and “hiccough” in the TRIP Database, Cochrane Database of Systematic Reviews, NICE and UpToDate in order to identify evidence-based recommendations on the management of this condition in PD.

Finally, we analyzed the official label (the Summary Product Characteristics in Europe and the US Package Insert in the USA) for the drugs most commonly recommended to treat hiccups to find out whether hiccups was an authorized use [15, 16]. We also checked whether PD appeared as a formal contraindication [15].

Results

Hiccups as an adverse drug reaction in the European pharmacovigilance database (EudraVigilance)

Considering hiccups associated with any drug, 1723 cases were found in EudraVigilance. The vast majority of these cases occurred in male patients: 1291 in men vs 364 in women.

A dopamine agonist was involved in 32 of these cases (Table 1), and among this group, 22 were in male patients. The mean age in this group was 73 ± 9 years. Japan and France were the countries that provided the most cases, with five notifications from each. Twenty-four of the 32 cases occurred in PD patients, while in six notifications, patients had restless legs syndrome (RLS), and in the other two, no clear diagnosis was described in the report. Pramipexole was the most frequently implicated drug, appearing in 16 reports (50%), followed by rotigotine with 6 notifications (19%), levodopa with 5 (16%), pergolide with 2 (6%), ropinirole with 2 (6%), and piribedil with 1 (3%). More than a half of the events (56%) were considered severe. In nine cases, patients developed a disability, in seven cases, patients needed hospitalization, and in one case, the patient died.

We found five cases of hiccups affecting PD patients where the suspicious agents were not a dopamine agonist, all of them in male patients (Table 1 supplementary data). All but one of

these events (80%) were considered severe. Two patients needed hospitalization, one developed a disability, and the other died.

As shown in Table 2, we calculated PRRs to assess the association between exposure to dopaminergic agonists (pramipexole, rotigotine, or levodopa) and hiccups. Both rotigotine and pramipexole met the criteria to generate a safety signal, suggesting that this adverse event (hiccups) is reported relatively more frequently in association with these drugs than with other medicinal products. The association was strongest for rotigotine, with a PRR of 9.59 and a 95% CI of 4.31 to 21.35.

Review of the literature

We found a total of 14 cases of hiccups associated with dopamine agonists published in the literature (Table 2 supplementary data). All of them were described in male patients. The mean age in this group was 74 ± 6 years. The first report of hiccups associated with dopamine agonists came from an analysis of the French Pharmacovigilance Database carried out in 1999 [2]. This analysis identified five cases, piribedil being involved in three notifications and levodopa in two. We also found another seven studies which described a further nine cases in which hiccups were associated with dopamine agonists. Pramipexole is the dopamine agonist drug most frequently involved in cases of hiccups and PD published in the literature, appearing in four reports [3, 4, 7, 8], while levodopa appeared in three cases [5, 6, 17], pergolide in one case [3], and piribedil in another case [7].

Review of hiccup treatment and management in PD

After reviewing the main available clinical guidelines of the literature on hiccups, we were not able to find any specific recommendations on the management of this condition in PD [18–20].

The only formally approved drugs for treating hiccups are haloperidol in the EU and chlorpromazine in the USA. Sadly, both drugs are formally contraindicated in PD according to their respective labels [15, 16]. Therefore, the use of all other drugs frequently administered for hiccups, including metoclopramide, gabapentin, amantadine, baclofen, amitriptyline, and carbamazepine, should be considered off-label.

Discussion

Our findings show, for the first time, a disproportionality in the reporting of hiccups in patients treated with dopamine agonists, which supports and extends the evidence suggesting that these drugs are associated with this

Table 1 Dopamine agonists associated with hiccups in Eudravigilance database

Suspicious drug	Year	Age	Sex	Country	Causality	Severity	Disease	Observations	
Pramipexole	2007	75	M	Belgium	Doubtful	Yes	PD	–	
	2008	66	M	Japan	Probable	No	PD	–	
	2009	81	M	Germany	Probable	No	PD	–	
	2009	69	F	Chile	Possible	No	PD	–	
	2010	62	M	Italy	Probable	No	PD	(Moja et al. [8])	
	2010	64	F	Japan	Doubtful	No	PD	–	
	2011	75	F	UK	Doubtful	Yes	PD	–	
	2012	–	M	Japan	Possible	No	PD	–	
	2013	66	M	Sweden	Possible	Yes	PD	–	
	2013	65	M	Sweden	Possible	Yes	PD	–	
	2013	66	M	Germany	Possible	No	PD	–	
	2008	83	M	USA	Possible	No	RLS	–	
	2009	–	F	France	Doubtful	No	RLS	–	
	2009	75	M	Netherlands	Possible	No	RLS	–	
	2010	79	M	Belgium	Doubtful	Yes	RLS	Latency 3 h	
	2012	52	F	Netherlands	Probable	No	RLS	Latency 2 days	
	2010	68	M	Netherlands	Probable	No	–	–	
	Rotigotine	2013	75	F	Japan	Probable	No	PD	Latency 30 min
		2013	80	M	Italy	Doubtful	No	PD	–
2014		73	M	France	Possible	Yes	PD	Latency 15 days	
2014		85	M	UK	Doubtful	Yes	PD	–	
2016		96	F	UK	Possible	Yes	PD	–	
2014		68	M	USA	Possible	Yes	RLS	–	
Levodopa	2004	75	M	France	Doubtful	Yes	PD	–	
	2008	72	M	UK	Doubtful	Yes	PD	(Wilcox et al. [17])	
	2011	65	F	France	Doubtful	Yes	PD	–	
	2014	70	F	Russia	Doubtful	Yes	PD	–	
	2015	77	M	Germany	Doubtful	Yes	PD	–	
Ropinirole	2005	74	F	USA	Possible	Yes	PD	–	
	2014	63	M	Switzerland	Possible	Yes	PD	–	
Pergolide	2001	79	M	Japan	Probable	Yes	PD	–	
	2006	76	M	USA	Probable	Yes	PD	(Sharma et al. [3])	
Piribedil	2013	84	M	France	Possible	Yes	–	–	

M male, F female, UK United Kingdom, USA United States of America, PD Parkinson s disease, RLS restless legs syndrome

adverse event. Both pramipexole and rotigotine met the criteria to generate a safety signal, the association being strongest for rotigotine, with a PRR of 9.59 and 95% CI of 4.31 to 21.35. This disproportionality analysis should be recognized to be only exploratory in the context of signal detection, as it does not allow a quantification of the true risk. Nevertheless, we consider that this finding warrants further investigation.

Another notable finding is the high percentage of male patients among cases of hiccups reported to Eudravigilance both in general and in the cases in which dopamine agonists were the implicated drugs. This is in line with the results of the systematic review carried out by Lee et al. [21], who

reported a male predominance (88.3%) after reviewing all studies about hiccups published between January 1990 and December 2013. This disproportion mainly occurred in hiccups of non-central nervous system (CNS) origin, such as those caused by drugs like dexamethasone [21]. The authors showed that this gender difference for hiccups was strongly associated with hiccups of non-CNS origin (OR 11.72, $P < 0.001$), whereas there was no significant association when the condition was of CNS origin (OR 1.74, $P = 0.072$).

We believe that the slightly higher prevalence of PD disease in male patients [22] is not sufficient to explain the disproportion of hiccup cases affecting male PD

Table 2 PRRs for dopamine agonists and hiccups in EudraVigilance

Dopamine agonist	PRR (95% CI); number of reports
Pramipexole ^a	5.34 (3.31–8.61); <i>n</i> = 17
Rotigotine ^a	4.31 (9.59–21.35); <i>n</i> = 6
Levodopa	1.38 (0.62–3.07); <i>n</i> = 6

^a Fulfill criteria to generate a safety signal. Lower boundary of PRR ≥ 1 and number of individual cases ≥ 3

patients found in our study. We hypothesize that dopamine agonists provoke hiccups affecting afferent or efferent nerves in the hiccup reflex arc rather than acting in the CNS and that male patients are more susceptible than women to this effect.

We also found that the great majority of the cases of hiccups associated with dopamine agonists found in EudraVigilance (91%) are not available in the published literature. Specifically, only three cases had been published in the biomedical literature [3, 8, 17]. This underlines the fact that the analysis of pharmacovigilance databases can provide valuable information for clinicians and researchers, since many notifications are only recorded there. On the other hand, spontaneous notification does not allow for a precise estimation of the real number of cases of hiccups, because of underreporting and the risk of incomplete information in such reports. Therefore, information provided by pharmacovigilance databases only represents a small sample of what occurs in a whole population [23].

Finally, we have to consider that the appearance of hiccups in a patient with PD may be problematic because many of the frequently used drugs for treating intractable hiccups are formally contraindicated in the disease due to their liability to worsen motor symptoms. Authors of a recently published study note that medication errors, including contraindicated antidopaminergic drugs, such as haloperidol, have a deleterious effect on PD patients [24]. Specific recommendations on the management of this potentially debilitating symptom in PD (as there are for psychotic and gastrointestinal symptoms) would be warmly welcomed.

In conclusion, analysis of data from the EudraVigilance database has allowed us to detect, firstly, a safety signal for rotigotine and pramipexole and hiccups, which supports the evidence that these drugs are associated with this adverse effect, and secondly, a male predominance in reported cases of hiccups both in general and in cases associated with dopamine agonists. Our results also highlight the need to include specific recommendations in clinical guidelines on how to manage hiccups in PD patients.

Author contributions Unax Lertxundi, Ana Marquinez, Saioa Domingo-Echaburu, Maria Angeles Solinis, Ana del Pozo, Begoña Calvo, Montserrat Garcia, and Carmelo Aguirre participated in the conception, manuscript preparation, writing the first draft, and the review and critique of the manuscript. Montserrat Garcia and Carmelo Aguirre searched for hiccup cases in Eudravigilance database.

Compliance with ethical standards

Financial disclosures Financial disclosure related to research covered in this article: The Departamento de Salud. Gobierno Vasco provided a grant of 20.300€ to the investigators.

Conflict of interest The authors declare that they have no conflict of interest.

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