SHORT COMMUNICATION

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Drug-Induced Yawning
A Review of the French Pharmacovigilance Database

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Abstract

Objective: To review the reports with 'yawning' as an adverse drug reaction (ADR) reported into the French Pharmacovigilance Database.

Methods: All the observations with 'yawning' reported in the French Pharmacovigilance Database until December 2004 were reviewed. We recorded drug(s) involved, characteristics of patients (age, sex and underlying disease) and of ADR (seriousness, delay in occurrence, evolution, imputability).

Results: Twenty-eight reports were recorded between 1985 and December 2004. The sex ratio of the patients included in these reports was 1.5 and the mean age was 46.2 (2–78) years. Thirty-eight drugs were involved, mainly serotoninergic agents (serotonin reuptake inhibitors [12]), dopaminergic agents (levodopa [3], dopamine agonists [3], monoamine oxidase B inhibitor [1]), opioids (morphine [1], methadone [1], buprenorphine [1], dextromethorphan [1]), benzodiazepines (4) and sodium channel inhibitors (lidocaine [2], flecainide [1]). Four ADRs were rated 'serious' (leading to hospitalisation). Patient outcome was usually favourable after drug withdrawal.

Conclusion: Despite its necessary methodological drawbacks (mainly under-reporting), this study reveals that several drugs may induce yawning in humans. Our work also indicates that stimulation of central dopamine or serotonin receptors elicits yawning in humans. This study underlines the role of several drugs in yawning and shows that this ADR is not systematically listed in the summary product characteristic even when it can be explained by the pharmacodynamic properties of the drugs.

Background

Yawning is a complex stereotyped behaviour, the physiological function of which remains unknown. It can occur in different physiological (i.e. sedation, hunger, hypoglycaemia) or pathological (neurological, infectious metabolic, psychiatric) circumstances. Several neurotransmitters are involved, such as dopamine, acetylcholine, serotonin or peptides. However, drugs that induce such behaviour in humans remain badly identified. In this article, we investigate the observations of 'yawning' as an adverse drug reaction (ADR), reported in the French Pharmacovigilance Database up to December 2004.

Methods

The French Pharmacovigilance System, established in 1973, consists of a network of 31 regional centres of pharmacovigilance. The French Pharmacovigilance Database was established in 1985 to register spontaneous reporting of ADRs.[1,2] Drug causality assessment is carried out by the French imputability method according to the time to onset and course of reaction, risk factors and screening for other causes. The score of imputability is classified into five levels: 'unlikely', 'possible', 'probable', 'likely' and 'certain'.[3]

Results

From 1985 to December 2004, 28 reports of drug-induced yawning were registered in the French Pharmacovigilance Database from a total of 173 055 reports. The sex ratio of the patients documented in the reports was 1.5 and the mean age was 46.2 years (range 2–78 years). Several underlying diseases were observed: depression and Parkinson's disease, psychosis, epilepsy, pharmacodependance and arterial hypertension. For each observation others reasons for yawning (hypoglycaemia, metabolic or neurological diseases) were excluded.

The 28 reports involved a total of 38 drugs (table I). Twenty-six different drugs were involved. The majority (n = 12) of reports involved serotonin reuptake inhibitors, followed by dopaminergic agents (n = 7), opioids (n = 4) benzodiazepines (n = 4) and sodium channel inhibitors (n = 4) drugs. Concerning opioids, one observation reported yawning occurring after morphine withdrawal, another case occurred after an abuse of buprenorphine in a patient already treated by methadone and another case was observed after intoxication in a young child caused by a cough mixture, which contained dextromethorphan.

The ADR was 'unexpected' for most of the drugs (n = 29). Imputability was rated 'possible' for 35 drugs, 'probable' for zuclopenthixol and lidocaine and 'likely' for only one drug (sertraline).

Four ADRs were rated as 'serious', leading to hospitalisation (one patient taking fluoxetine and metoclopramide, one taking dextromethorphan, one taking lidocaine and one taking methylergometrine).

The delay of occurrence largely varied from 30 minutes to several months after the introduction of the drug. For example, several months were necessary between introduction of dopaminergic drugs and the occurrence of yawning. This delay was longer for benzodiazepines: 1 month to several years.

When the suspected drugs were stopped, a positive dechallenge was observed most of the time: this was observed in 18 cases for 21 drugs withdrawn. The ADR disappeared without the implicated drug being stopped in five observations; the implicated drugs here were dopaminergic agents (levodopa [1], selegiline [1], ropinirole [1]), methadone (1) and paroxetine (1).

Discussion

Drug-induced yawning is rarely mentioned in pharmacological textbooks.[4,5] Antidepressants, in particular serotonin reuptake inhibitors, are drugs that have been implicated in excessive yawning.[6] This ADR is mentioned in the summary product characteristic of several drugs from this pharmacological class. It has also been reported when starting a dopamine receptor agonist (like apomorphine,[7] pergolide[8] or ropinirole). Other drugs known to induce excessive yawning are acetylcholinesterase inhibitors, corticotrophin, ovulation inductors and sodium valproate.[9,10]

From 1985 to December 2004, only 28 cases of yawning as ADR were reported in the French Pharmacovigilance Database. Evaluation of spontaneous reporting does not permit quantitative evaluation of the frequency of yawning as an ADR. To determine the real incidence of this ADR, the number of patients taking each drug involved would need to be known. Unfortunately, this information is not available in the French Pharmacovigilance Database. However, spontaneous reporting systems remain useful tools for gaining a better understanding of drugs and for detecting new ADRs.[11,12]

The small number of observations in our study could reflect both a low incidence of yawning in

Table I. Description of the 38 drugs implicated in inducing yawning (data from the French Pharmacovigilance Database)

Pharmacological class	Overall no.	Implicated drug (no. of cases)	Expected ADRs	Imputability score (no. of cases)	Seriousness (no. of cases)	Delay of occurrence	Drug withdrawal (no. of cases)	Resolution (no. of cases)
Serotonin reuptake inhibitor	12	Paroxetine (5)	No	'Possible' (5)		1 day to 4wk	Yes (3)	Yes (4)
		Fluoxetine (4)	Yes	'Possible' (4)	Hospitalisation (1)[a]	3 wks to 1y	Yes (3)	Yes (3)
		Sertraline (3)	Yes	'Likely'(1); 'Possible'(2)		3 days to 8wk	Yes (2)	Yes (2)
Dopaminergics	7	Levodopa (3)	No	'Possible' (3)		2mo to 4y	No (3)	Yes (1)
		Bromocriptine (1)	No	'Possible'		5mo	No	No
		Pergolide (1)	No	'Possible'		6mo	No	No
		Selegiline (1)	No	'Possible'		3mo	No	Yes
		Ropinirole (1)	No	'Possible'		2mo	No	Yes
Opioids	4	Morphine (1)	No	'Possible'		10wk	Yes	Yes
		Methadone (1)[b]	No	'Possible'		12wk	No	Yes
		Buprenorphine (1)[b]	No	'Possible'		1h	Yes	Yes
		Dextromethorphan (1)	No	'Possible'	Hospitalisation	2 days	Yes	Yes
Benzodiazepines	4	Clonazepam (1)	No	'Possible'		Several years	No	No
		Lorazepam (1)	No	'Possible'		Not reported	Yes	Yes
		Prazepam (1)	No	'Possible'		4wk	Yes	No
		Zoplicone (1)	No	'Possible'		3y	No	No
Sodium channel inhibitors	3	Lidocaine (2)	Yes	'Probable' (1); 'Possible' (1)	Hospitalisation (1)	10 min to 1 day	Yes (2)	Yes (2)
		Flecainide (1)	No	'Possible'		3mo	No	No
Others	8	Atorvastatin (1)	No	'Possible'		7mo	Yes	Yes
		Domperidone (1)	No	'Possible'		2y	Yes	Yes
		Follitropin (1)	No	'Possible'		3h	Yes	Yes
		Isotretinoin (1)	No	'Possible'		?	No	No
		Methylergometrine (1)	No	'Possible'	Hospitalisation	8h	Yes	Yes
		Metoclopramide (1)	No	'Possible'	Hospitalisation[a]	Not reported	Not reported	Not reported
		Toloxatone (1)	No	'Possible'		7 days	Yes	Yes
		Zuclopenthixol (1)	No	I2		2 days	Yes	Yes

a These hospitalisations refer to the same patient.

b These exposures occurred in the same patient.

ADRs = adverse drug reactions.

clinical practice and under-reporting of this reaction. It is well known that under-reporting is an important factor in a spontaneous reporting system and the extent of under-reporting depends on the characteristics of the particular ADR (seriousness, expected or unexpected).[13,14] Yawning is rarely a 'serious' ADR: in our study, only four patients were hospitalised and in one case this was because the yawning induced a jaw luxation. Moreover, yawning may not be reported to the pharmacovigilance system by health professionals because it is not frequently listed as an ADR in the summary product characteristics of drugs. This could explain why this ADR was rated as 'expected' in only 25% of our observations (n = 9). For example, yawning is mentioned as an ADR in the summary product characteristic for only one serotonin reuptake inhibitors among the three implicated in our cases. For sodium channel inhibitors, yawning is listed in the summary product characteristics of lidocaine but not flecainide, whereas two ADRs were registered in our study with lidocaine and one ADR with flecainide.

Although yawning was usually an 'unexpected' ADR, its occurrence could be explained in most of our observations by pharmacodynamic effects of drugs involved. In our study, serotonin reuptake inhibitors were the main pharmacological class involved, followed by dopaminergic drugs, underlining the excitatory effects of serotonin and dopamine on yawning described in experimental studies.[15-21] Three observations were available with opioids, involving four drugs. The inhibitory role of opioid system on yawning[22] could be confirmed by the case occurring after a morphine withdrawal. However, the two other cases occurred quickly after opioid abuse. Yawning occurring with benzodiazepines can be expected because of the sedative effect of these agents. Involvement of follitropin is understandable because of prefacilitatory action of sexual hormones on yawning.[23] Methylergometrine induced-yawning could be explained by its lateral action as a dopamine agonist.[24] The observation of yawning occurring with metoclopramide is more surprising since this drug is believed to act as a dopamine antagonist. However, this drug is also known to activate some subtypes of serotoninergic receptors (5-HT_4).[25] Thus, we suggest that metoclopramide could induce yawning through a serotoninergic activation. Moreover, this drug is a procaine-like agent, which can contribute to the effect of yawning. Domperidone should inhibit yawning, because it is a dopamine antagonist. In our study, one observation described yawning with domperidone. However, this could be explained by the fact that the patient was also receiving a benzodiazepine (lorazepam). The mechanism of drug-induced yawning is still unclear for other drugs in our study, for example atorvastatin and isotretinoin, which are not associated pharmacologically to other drugs implicated in causing this ADR.

Conclusion

The results of this study do not in themselves provide evidence of the mechanisms involved in drug-induced yawning, but lend some support to findings in experimental studies. Stimulation of central dopamine or serotonin receptors elicits yawning in humans. In contrast, the role of opioid systems seems inhibitory. Despite the methodological drawbacks of this study (mainly under-reporting), the drugs found to be involved in excessive yawning in our study can be compared with drugs already known to induce such an effect. This study underlines the role of several drugs in yawning and shows that sometimes ADRs, which can be explained by the pharmacodynamic properties of drugs, remain unknown since they are not listed in the summary product characteristics. This study underlines the role of several drugs in yawning and shows that this ADR is not systematically listed in the summary product characteristic even when it can be explained by the pharmacodynamic properties of the drugs.

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