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Drugs and Sleep Apneas? A review of the French Pharmacovigilance database

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sleep apnea; adverse drug reaction; pharmacovigilance; drug

Abstract – The present work reviews the case reports of drug-induced sleep apnea recorded in the French pharmacovigilance database. Notifications are very rare (around 1/100 000 notifications). This paper shows that sleep apnea can be aggravated or revealed by some drugs. Main drugs involved were psychotropics (benzodiazepines, neuroleptics) and opioids.

Mots clés :

apnée du sommeil ; effet indésirable médicamenteux ; pharmacovigilance ; médicament

Résumé – Médicaments et apnées du sommeil ? Une revue de la base française de pharmacovigilance. Ce travail examine les cas d'apnées du sommeil médicamenteuses enregistrées dans la base française de pharmacovigilance. Les notifications sont très rares (environ 1/100 000 notifications). Ce travail montre que les apnées du sommeil peuvent être aggravées ou révélées par certains médicaments, dont les principaux en cause sont les psychotropes (benzodiazépines, neuroleptiques) et les opioïdes.

Abbreviations: see end of article.

1. Introduction

Sleep apnea is a sleep disorder characterized by pauses in breathing or instances of shallow or infrequent breathing during sleep.^[1-3]

It is highly relevant to patients with arterial hypertension and recent data suggest that it represents the most prevalent secondary cause to high blood pressure in patients with resistant hypertension.^[4] Beside arterial hypertension, sleep apnea was found to be associated with an increased risk of heart failure, coronary arterial disease and myocardial infarction, pulmonary hypertension, stroke and arrhythmias.^[5] Several forms of sleep apnea were described according to their mechanism: central, obstructive and mixed subtypes

corresponding to 0.4%, 84% and 15% of cases respectively.^[6] The best test for diagnosis of sleep apnea syndrome is overnight polysomnography with the measure of apnea-hypopnea index.^[1-3]

Male gender, overweight or obesity, age over 40, a large neck size, enlarged tonsils or tongue, small jaw bone, family history, gastroesophageal reflux or alcohol intake were described as risk factors.^[1-5] In contrast, as far as we know, very few studies have investigated the putative role of drugs in the occurrence of this symptom.

Thus, it was the aim this study to investigate a potential role for drugs using spontaneous notifications recorded in the French pharmacovigilance database (FPVD).

Tableau I. Main characteristics of the 6 notifications with sleep apnea in the French pharmacovigilance database between 1985 and 2014.

	Age (year)	G	Medical history	Suspected drug(s)	SPC	Concomitant drug	SPC	Evolution	I
1	70	M	Arterial hypertension	Losartan + hydrochlorothiazide	No	Pipobroman Venlafaxine	No No	Favorable after drug withdrawal	I1
2	?	M	HIV, opiate dependence	Cyamemazine Ritonavir Lamivudine Amprenavir Abacavir	No No No No No	Buprenorphine Venlafaxine Clorazepate Acepromazine Aceprometazine	No No Yes No	Unknown	I1 I1 I1 I1 I1
3	31	M	BMI = 29 Chronic psychosis, sleep apnea, alcohol, cannabis, benzodiazepine dependence, smoking	Cyamemazine Clonazepam	No Yes	Hydroxyzine Lithium Alimemazine Amisulpride	No No No No	Unknown	I1 I1
4	40	M	Unknown	Piroxicam	No		No	Positive rechallenge Favorable after drug withdrawal	I3
5	48	M	Sleep apnea	Tramadol	No		No	Favorable after drug withdrawal	I1
6	38	F	Narcolepsy Catalepsy	Sodium oxybate	Yes	Methylphenidate	No	Unknown	I1

The column SPC (as recorded in the French public database of drugs of the French Drug Agency) indicates if sleep apnea was mentioned (yes) or not (no) in the drug SPC. The imputability level (I) was defined according to the French method.^[7]

BMI: body mass index; **F:** female; **G:** gender; **HIV:** human immunodeficiency virus; **I:** imputability level; **M:** male; **SPC:** summary of product characteristics

2. Methods

FPVD was previously described elsewhere.^[7] Since 1985, it includes all spontaneous notifications of adverse drug reactions (ADR) reported by French health professionals (and by patients since June 2011) to the French network of the 31 regional pharmacovigilance centers. These records include the main characteristics of patients suffering from the ADR (age, gender, medical history), drug(s) received by the patient (name, date of beginning, definition as “suspect” or “concomitant”) as well as the ADR (kind, date of occurrence, seriousness, evolution) with the causality (imputability) level classified according to the French method from 0 (“excluded”) to 4 (“very likely”).^[8]

For the present work, we recorded all case report with the key word “sleep apnea” (whatever the level of imputability) registered in the FPVD between the 1st January 1985 and the 30th June 2014. For each observation, age, gender and medical history of the patient were registered. Only “suspect” drug(s) with their imputability level were recorded.

For each suspect or concomitant drug, we also investigated if the word « sleep apnea » appeared in the summary of product char-

acteristics (SPC), as described in the French public database of drugs of the French drug agency.^[9]

3. Results

Among the 538 967 case reports recorded in the FPVD during these 29 years, only 9 ADR were registered as “sleep apnea”. After reviewing these 9 case reports, 3 were excluded because they did not correspond to the definition of “sleep apnea”, but rather to breathing depression occurring during sleep and following drug overdoses.

The 6 case reports mainly occurred in males (5/6). Mean age was 45.4 years (range 38-70; unknown in 1 case). Table 1 summarizes the main characteristics of the 6 case reports and indicates if the ADR was (or not) described in the French public database of drugs.

4. Discussion

The present study was an exploratory and preliminary one, performed in order to investigate if drugs could be described as a cause

of sleep apnea, an etiology that is not clearly described in the literature.^[1-6] For the first time, it shows that several groups of drugs can aggravate or reveal such a syndrome. Despite the well-known problem of underreporting in pharmacovigilance, reports of sleep apnea as ADR appears to be very rare into a pharmacovigilance database (1.1/100 000 notifications in the FPVD). However, both the characteristics of spontaneous notifications and the difficulties of diagnosis for sleep apnea did not allow concluding about frequency and prevalence of this ADR. Moreover, the necessity to use a polysomnographic test for the true diagnosis can also explain this underreporting. In fact, it must be underline that such a polysomnographic record was not clearly described in the 6 case reports in the FPVDB.

From a clinical point of view, it is important to underline that evolution was always favorable after drug withdrawal (when it was known, 3 cases out of 6), which is a further argument for involvement of drugs in these ADR reports. These case reports of sleep apnea related to drugs mainly occurred in males, thus confirming male gender as a risk factor for sleep apnea. The role of associated factors must be also underlined since this ADR occurred in patients with previous medical history, especially 3 with sleep disorders (2 sleep apneas, 1 narcolepsy), 2 with drug dependence and 1 with arterial hypertension. These diseases are known as associated or risk factors for sleep apnea.^[1-6] This suggests that drugs can be considered as aggravating or promoting factors for sleep apnea in predisposed patients.

From a pharmacodynamic point of view, it is possible to discuss the putative role of some drugs in this ADR. "Suspect" drugs belong to several pharmacotherapeutic classes: angiotensin receptor antagonists (losartan), thiazide diuretics (hydrochlorothiazide), neuroleptics (cyamemazine, found 2 times), protease inhibitors (ritonavir, amprenavir), nucleosidic analogs (lamivudine, abacavir), non-steroidal antiinflammatory agents (piroxicam), benzodiazepines (clonazepam), opioids (tramadol) and central depressants (sodium oxybate). Among these drugs, the word « sleep apnea » was only found for clonazepam (as contraindication) and sodium oxybate (as use precaution) in the French public database of drugs.^[9] However, in several observations, the potentiating role of associated ("concomitant") drugs cannot be ruled out. It is the case, for example, for psychotropic drugs: antidepressant in observations 1 and 2, opioid in observation 2, association of benzodiazepine + 2 H1 antihistamines in observation 2 and other H1 antihistamines, lithium plus neuroleptic in observation 3. Sleep apnea is mentioned as contraindication for the association clorazepate + acepromazine + aceprometazine (Noctran[®]) in the French public database of drugs.^[9]

In fact, the depressive effect of benzodiazepines on the respiratory system is well known^[10] and one case of sleep apnea with sodium oxybate was described in a 39-year-old woman without previous symptom.^[11] The role of opioid drugs is also expected since the depressive effect of morphine and related drugs on central respiratory control is well documented.^[12] Several publications

reported cases of sleep apnea with opioids.^[13-15] Among opioid drugs, our work involves tramadol (but also probably buprenorphine, as a concomitant drug).

Involvement of neuroleptic drugs is also plausible although the ADR mechanism is difficult to explain: we can suggest a sedative effect related to their antagonistic effect on H1 histamine receptors.^[16] Further studies are necessary.

In contrast, the role of the other pharmacological classes remains unknown. As far as we know, none publication has previously described such an ADR with angiotensin receptor antagonists, thiazide diuretics or antiretroviral drugs. However, one could underline that these two observations included venlafaxine as a concomitant (associated) drug. One observation reported a case of sleep apnea syndrome in a 50-year-old man receiving venlafaxine + trazodone.^[17] The central depressive effects of antidepressants could be suspected.

The observation with the non-steroidal antiinflammatory agent (piroxicam) is also surprising despite a positive rechallenge. This effect could be related to piroxicam-induced fluid retention, since non-steroidal antiinflammatory agents are known to reduce renal blood flow and sodium excretion and enhance the antidiuretic effect of vasopressin.^[18] In fact, some cases of respiratory depression or even apnea were described with overdoses of fenoprofen, ibuprofen or naproxen.^[19] The problem is complex since some inhaled corticosteroids were proposed in the treatment of sleep apnea.^[20]

In conclusion, this paper suggests that sleep apnea can be aggravated or revealed by some drugs and especially psychotropic (benzodiazepines, neuroleptics and perhaps also antidepressants) or opioid drugs. Prescription of these drugs should be careful in patients suffering from sleep apnea. Further data on larger databases are necessary to better define drugs potentially involved in sleep apnea. Finally, this work suggests the interest of better notifications on this unknown ADR.

Conflict of interest. None declared by the authors.

Abbreviations. ADR: adverse drug reactions; FPVD: French pharmacovigilance database; SPC: summary of product characteristics.

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