

ORIGINAL
ARTICLEOverview of adverse reactions to nefopam:
an analysis of the French Pharmacovigilance
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pharmacovigilanceReceived 30 June 2006;
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accepted 15 March 2007*Correspondence and reprints:
durrieu@cict.fr**ABSTRACT**

Nefopam is widely used for the relief of moderate acute pain. Its safety profile remains to be specified. The objective of the study was to review adverse reactions to nefopam spontaneously reported to the French Pharmacovigilance system. All cases of adverse drug reactions (ADRs) associated with nefopam, registered in the French Pharmacovigilance database from January 1, 1995 to December 31, 2004, were reviewed. For each reported ADR, information about patient (age, gender, medical history), drug exposure (suspected and concomitantly used drugs), characteristics of ADRs (imputability score, time of onset, seriousness, outcome) were collected. A total of 114 ADRs with an imputability rated from 'plausible' (I2) to 'likely' (I3) and 'very likely' (I4) was analysed. The most frequent ADRs included 'expected' ADRs such as sweating, nausea, tachycardia, malaise or vomiting; 61 ADRs were 'unexpected'. No overdose was reported; 26 ADRs (23%) were considered as 'serious'. Most of them were 'unexpected', including neuropsychiatric (hallucinations, convulsions) or cutaneous (pruritus, erythema, urticaria) ADRs. Six cases of anaphylactic ADRs (two angioedema and four anaphylactic shocks) were reported, all occurring shortly after use of nefopam during the post-operative period. Physicians should be aware of the possible occurrence of some serious ADRs when using nefopam such as convulsions and anaphylactic shocks, especially when the drug is used in special medical conditions, like post-operative periods.

INTRODUCTION

Nefopam, marketed since 1981 in France, is a centrally acting non-opioid analgesic, structurally related to diphenhydramine (an H1 antihistamine drug) and orphenadrine (an antimuscarinic drug). The precise mechanisms underlying the pharmacological actions of nefopam remain unclear. In vitro and in vivo studies indicate that its analgesic properties may be related to inhibition of serotonin, epinephrine and dopamine synaptosomal uptake [1]. Recent evidence also suggests a possible action of nefopam on the central

neurotransmission mediated by glutamate. Experimental studies have shown that nefopam inhibits calcium influx, cGMP formation and N-methyl-D-aspartate (NMDA) receptor-dependent neurotoxicity following activation of voltage-sensitive calcium and sodium channels [2]. Nefopam is widely used for the relief of moderate acute pain, mainly in the post-operative period. As far as we know, the few studies investigating the safety profile of this drug were relatively old [3,4]. The objective of the study was to review adverse reactions to nefopam spontaneously reported to the French Pharmacovigilance system.

SUBJECTS AND METHODS

The study was based on spontaneous reports of adverse drug reactions (ADRs) submitted to the French Pharmacovigilance system. Reporting 'serious' or 'unexpected' ADRs (as defined by Edwards and Aronson [5,6]) to the 31 French Regional Centers is mandatory for any prescriber, pharmacist, dentist or midwife in France. ADRs are coded according to the ADR Terminology. All cases of ADRs associated with nefopam, registered in the French Pharmacovigilance database from January 1, 1995 to December 31, 2004, were reviewed. For each reported ADR, we noted information about patient (age, gender and medical history), drug exposure (suspected and concomitantly used drugs) and characteristics of ADRs (time of onset, imputability score, seriousness and outcome). Imputability (a causality assessment score) was evaluated according to the official French methodology [7] and rated according to an imputability decision scale ranging from 'unlikely' (I0), 'possible' (I1), 'plausible' (I2), 'likely' (I3) and 'very likely' (I4). 'Expected' ADRs were defined as adverse events described in the French summary of product characteristics. For nefopam, they included nausea, vomiting, sweating, somnolence, malaise, urinary retention, dizziness, irritability, nervousness, dry mouth, vertigo, tachycardia and palpitations.

RESULTS

A total of 324 ADRs causally related to nefopam was identified in the whole French Pharmacovigilance database from 1995 to 2004. All reports were analyzed. ADRs with a 'possible' imputability (I1) were not selected. Thus, 114 ADRs with an imputability rated from 'plausible' (I2) to 'likely' (I3) and 'very likely' (I4) were analysed. Most of them (97) were reported between 2000 and 2004. The main characteristics of the patients and the ADRs are described in *Table I*.

No overdose was reported. The most frequent ADRs included 'expected' ADRs, such as sweating (15 cases), nausea (10 cases), tachycardia (eight cases), malaise (six cases) or vomiting (five cases). Sixty-one ADRs were 'unexpected', including hallucinations (11 cases), confusion (11 cases), cutaneous (erythema: seven cases; pruritus: four cases; urticaria: three cases) or anaphylactic (six cases) ADRs.

Twenty-six ADRs (23%) were considered as 'serious'. One patient experienced fatal convulsions related to administration of nefopam alone (imputability score:

Table I Nefopam-induced ADRs reported in the French Pharmacovigilance database from 1995 to 2004: main characteristics.

<i>Patients</i>	
Number of patients	62
<i>Age (years)</i>	
Mean (SD)	51.6 (20.9)
Range	13–90
<i>Gender</i>	
Male, <i>n</i> (%)	32 (51.6)
Female, <i>n</i> (%)	29 (46.8)
Not specified	1 (1.6)
<i>Comedications</i>	
None (monotherapy), <i>n</i> (%)	9 (14.6)
One, <i>n</i> (%)	10 (16.1)
More than one, <i>n</i> (%)	39 (62.9)
Not stated, <i>n</i> (%)	4 (6.4)
<i>ADRs</i>	
Number of ADRs	114
<i>Dates of reports</i>	
1995–1999	17
2000–2004	97
<i>Type</i>	
Expected, <i>n</i> (%)	53 (46.5)
Unexpected, <i>n</i> (%)	61 (53.5)
<i>Imputability, <i>n</i> (%)</i>	
Plausible (I2)	74 (64.9)
Likely (I3)	36 (31.6)
Very likely (I4)	4 (3.5)
<i>Seriousness, <i>n</i> (%)</i>	
Serious	26 (22.8)
Non-serious	87 (76.3)
Not stated	1 (0.9)
<i>Outcome, <i>n</i> (%)</i>	
Without sequelae	108 (94.7)
With sequelae	0
Death	1 (0.9)
	(one patient with convulsions)
Not stated	5 (4.4)

Only reports with an imputability scale $\geq$ plausible (I2) are shown in this table.

'likely'). All other ADRs disappeared without sequelae. Serious ADRs ($n = 26$) are described in *Table II*. They were considered as 'expected' in only one case. Most of them were 'unexpected' including neuropsychiatric (hallucinations, convulsions, confusion, delirium), cutaneous (erythema, pruritus, urticaria). One case of arterial hypotension and another one with heart failure were also enregistered in this 'unexpected' group of ADRs. Anaphylactic ADRs were reported in 6 cases: two angioedema and four anaphylactic shocks (described in *Table III*). The anaphylactic shocks all occurred shortly after nefopam administration during the post-operative period. History

Table II Nefopam-induced 'serious' ADRs reported in the French Pharmacovigilance database from 1995 to 2004.

Serious ADRs	Number	Imputability score
<i>Expected</i>		
Cardiovascular		
Tachycardia	1	I2
<i>Unexpected</i>		
Neuropsychiatric		
Confusion	1	I2
Hallucinations	3	I3, I2, I2
Convulsions	2	I3, I2
Delirium	1	I3
Cutaneous		
Pruritus	2	I2, I2
Urticaria	2	I3, I4
Erythema	3	I2, I2, I2
Anaphylactic		
Angioedema	2	I3, I4
Anaphylactic shock	4	I3, I3, I3, I4
Cardiovascular		
Heart failure	1	I3
Arterial hypotension	1	I3
Miscellaneous		
Syncope	1	I3
Mydriasis	1	I2
Dyspnea	1	I3

I2, 'plausible'; I3, 'likely'; I4, 'very likely'.

of allergic reaction was only reported in two patients. The role of co-administered drugs cannot be ruled out, as ketoprofen and paracetamol (and amoxicillin in one case) are also known to induce such an ADR.

DISCUSSION

The aim of the study was to focus on the safety profile of nefopam. In fact, few studies have investigated nefopam-

induced ADRs [3,4]. In 1980, Heel et al. [3] described sweating, nausea and sedation as the most frequent ADRs in patients treated with nefopam. Pillans and Woods [4] reviewed spontaneous reports of ADRs related to nefopam received by the New Zealand Pharmacovigilance system over a 12-year period (1982–1994). Since 1995, no accurate data on nefopam-induced ADRs have been reported. As a result of this, relatively few number of papers and the recent concomitant increase in its consumption (a sixfold increase for the period from 2000 to 2004 compared with the period from 1995 to 1999 in France; unpublished data given by French Health Products Agency, AFSSAPS), we decided to review nefopam-induced ADRs as reported in the French Pharmacovigilance database. In order to eliminate confounding factors, we only selected ADRs with imputability scored as 'plausible' (I2), 'likely' (I3) or 'very likely' (I4).

Our study found some interesting results. First, besides 'expected' ADRs (such as nausea, vomiting, malaise, excessive sudation, somnolence, palpitations, tachycardia and vertigo, often related to the anticholinergic properties of the drug), the present study allows to describe some 'unexpected' (i.e. not previously labeled in the French SPC) ADRs considered as 'serious': neuropsychiatric (hallucinations, convulsions, confusion, delirium), cardiovascular (arterial hypotension, heart failure), cutaneous (erythema, pruritus, urticaria) and anaphylactic ADRs.

The neuropsychiatric and cardiovascular ADRs are mainly known as signs of overdose. They include confusion, convulsions, hallucinations, tachycardia, bundle branch block or cardiac arrest [8–11]. Three fatal cases after nefopam overdose, have been reported in the literature [8–10]. In these reports, the patients

Table III Characteristics of the anaphylactic shocks ($n = 4$) reported with nefopam in the French Pharmacovigilance database from 1995 to 2004.

No.	Date of report	Imputability	Age of patient (years)	Gender	Relevant history	Time to onset (hours)	Associated drugs	Outcome	Comments
1	2002	I3 (likely)	42	F	None	0.25	Ketoprofen, paracetamol	Resolved	Post-operative period
2	2002	I3 (likely)	21	M	Allergic reaction	0.10	Amoxicillin	Resolved	Post-operative period causal role of amoxicillin: 'likely'
3	2004	I3 (likely)	65	F	Allergic reaction	1	Ketoprofen, paracetamol, ketamine	Resolved	Post-operative period
4	2004	I4 (very likely)	56	F	None	2	Paracetamol	Resolved	Post-operative period. Positive cutaneous test to nefopam

exhibited most of the neurologic and cardiovascular ADRs listed above. Our findings show that these ADRs, especially convulsions and cardiac arrest, would also occur at normal therapeutic dosages. One ADR was fatal. A 72-year-old man suffering from nephritic colic, experienced convulsions 30 min following nefopam administration. Nefopam was the sole drug administered to this patient without relevant medical history. In the other patients, ADRs disappeared after withdrawal of nefopam. From a pharmacological point of view, the description of convulsions or cardiac arrest could indicate that nefopam interferes with membrane ionic channels in brain and in heart, as also suggested by its chemical structural analogy with carbamazepine or flunarizine [2].

Cutaneous ADRs and hypersensitivity manifestations were listed in literature as ADRs possibly related to nefopam, but no detailed description was reported [4]. In our review, serious cutaneous ADRs included pruritus, erythema and urticaria. In two cases, they were associated with angioedema or anaphylactic shock. They occurred shortly after nefopam administration, mainly in the post-operative period. They resolved after drug withdrawal and corrective treatment. Interestingly, our results show that hypersensitivity reactions can occur in patients without a history of allergic reaction.

In conclusion, this study enables us to specify the safety profile of nefopam, a drug which consumption widely increased in France during last years. Although our study could be criticized due to mandatory under-reporting associated with each pharmacovigilance study, it is interesting to underline that the number of ADRs reported to the French Pharmacovigilance system increased in the same way as the consumption of nefopam did. Physicians should be aware of the possible occurrence of some serious ADRs like convulsions, anaphylactic shocks with nefopam, especially when the

drug is used in special medical conditions, like post-operative periods.

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