

ORIGINAL
ARTICLE

Safety profile of etifoxine: A French pharmacovigilance survey

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Keywords

adverse drug reaction,
anxiolytic,
etifoxine,
pharmacovigilance

Received 14 April 2015;
revised 31 October 2015;
accepted 13 November 2015

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This manuscript has not been
previously published except in
the form of an abstract that
appeared in Drug Safety 2012;
35 (10): 877–970 (Abstract
P180).

ABSTRACT

Etifoxine chlorhydrate is a benzoxazine derivative approved for the treatment of psychosomatic manifestations of anxiety since 1979. Previously labeled adverse drug reactions (ADRs) only include drowsiness, benign cutaneous reactions, and acute hypersensitivity reactions. The objectives were to examine recent data on etifoxine-related ADR by reviewing Individual Case Safety Reports (ICSRs) recorded in France especially unexpected ADRs. Etifoxine-related ICSRs were extracted from the French Pharmacovigilance database from 1 January 2000 to 30 April 2012 and data from the marketing authorization holder up to 31 December 2011 were also obtained. Of the 350 cases retained for analysis, 123 (35%) were considered serious. Dermatological or acute hypersensitivity reactions were the most frequent ADRs (59%) mainly isolated cutaneous eruptions. However, there were 24 cases of severe toxidermia (DRESS in 5, erythema multiforme in 10 and Stevens–Johnson syndrome in 5) with etifoxine as the most suspected drug in 11 patients, and seven cases of vasculitis or serum sickness-like reaction. Liver disorders were reported in 34 patients of whom 25 developed acute hepatitis with a cytolytic biological pattern in 16. Other unexpected ADRs included 16 reversible cases of metrorrhagia with positive rechallenge in 5, and three cases of biopsy-proven microscopic colitis of which one recurred after etifoxine re-administration. Although etifoxine has been marketed for more than 30 years, this survey identified a number of unexpected and sometimes serious ADRs, in particularly severe toxidermia and acute cytolytic hepatitis. A recent update of the French etifoxine summary of the product characteristics (SPC) was based on these findings.

INTRODUCTION

Etifoxine chlorhydrate (Stresam^{  }; Biocodex Laboratories, Gentilly, France) is a benzoxazine derivative indicated in psychosomatic manifestations of anxiety, such as neurovegetative dystonia with cardiovascular

manifestations. The recommended oral daily dose is 150–200 mg. Although the anticipated therapeutic effects of etifoxine are close to those of benzodiazepines, its chemical structure is different and it does not bind to the benzodiazepine receptor. Accordingly, flumazenil does not reverse the anxiolytic effect of etifoxine

in vivo [1]. Etifoxine appears to produce anxiolytic effects by binding to the β_2 and β_3 subunits of the GABA-A receptor complex and/or by stimulating the production of neurosteroids that potentiate GABA-A receptor activity [2].

Etifoxine is mostly used in France and is also marketed in several African, East European and South America countries. Although it was approved in 1979, very few data on its safety are available and only drowsiness and acute hypersensitivity reactions (urticarial, angioedema) were labeled up to December 2014. As a wider range of ADRs recently emerged based on spontaneous notification, in particular acute hepatitis [3,4], we undertook an analysis of spontaneous notifications reported in France to more accurately delineate the safety profile of etifoxine.

METHODS

The French pharmacovigilance network consists of 31 Regional Pharmacovigilance Centers that collect and analyze spontaneous reports of ADRs from healthcare professionals and patients. All validated cases are stored in a common computerized database using MedDRA terminology for ADRs coding, the French Pharmacovigilance database (FPD). Cases where etifoxine was considered to be suspected or an interacting drug and with an ADR occurring between 1st January 2000 and 30th April 2012 were extracted from the FPD. In addition, French cases notified to the marketing authorization holder (MAH) between 1st January 2000 and 31st December 2011 were also obtained. Only medically confirmed reports were analyzed. All Individual Case Safety Reports (ICSRs) were carefully reviewed by a physician trained in pharmacovigilance. Only the main or most significant ADR for each case was retained for analysis. Cases in which the narrative contained insufficient information, cases related to pregnancy exposure and cases with other obvious drug-related or non-drug causes were excluded from the analysis. According to the recommendations of the International Committee on Harmonization from the WHO Collaborating Centers for International Drug Monitoring [5], serious ADRs were defined as a fatal or life-threatening adverse effect, or as an adverse effect that required patient hospitalization or prolongation of ongoing hospitalization, or resulted in persistent or significant disability. Particular attention was paid to the time to onset of the event in order to assess the causal relationship with etifoxine treatment carefully. Causal relationship assessment was scored

using the French drug reaction assessment method [6]. For severe cutaneous reactions and hepatic disorders, scoring or causality was assessed using recognized recommendations [7,8].

Data on sales and prescription were provided by the MAH and the French National Agency for Medicine and Health Products Safety (ANSM) for the years 2002–2011. The number of treatments sold during this period was calculated from prescription data using the mean duration of treatment (34.7 days) and the mean prescribed daily dose (143 mg) as follows: number of treatments = number of tablets sold/mean prescribed daily dose \times mean duration of prescription.

RESULTS

Of the 419 cases identified (84% from the FPD), 69 were excluded from the analysis. The 350 remaining cases involved 289 women (83%) and 57 men (gender unknown in 4). The median age was 40.5 years (range: 12–98) and most of the patients were 18–59 years of age (67%). A seriousness criterion was present in 125 cases (36%). Indications of etifoxine (available in 124 patients) were essentially anxiety (86.3%) and mood disorders (7.3%). The dose ($n = 208$) was within the approved range in 96.6% of cases with a median daily dose of 150 mg/day (range: 25–300). Only seven patients were treated with doses higher than 200 mg/day. Although etifoxine sales more than doubled between 2002 and 2009, the number of reports per million treatments remained stable during this period of time (Figure 1) with an incidence

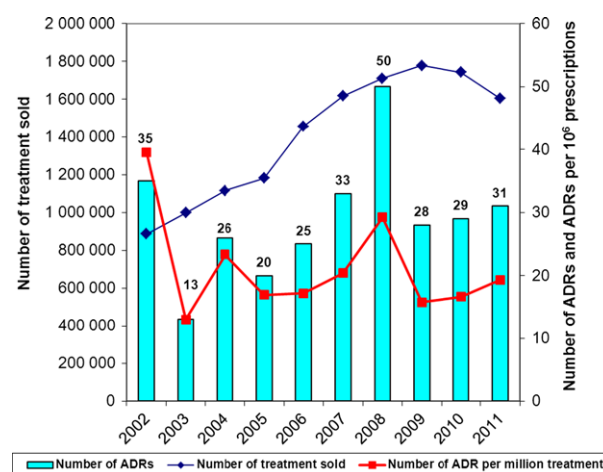


Figure 1 Sales, spontaneous notifications, and incidence rate of etifoxine ADRs.

ranging from 13 to 39.5 per 10⁶ treatments (mean: 21.3) for all cases, and from 3 to 14 per 10⁶ treatments for serious cases.

As shown on Figure 2, dermatological and hypersensitivity reactions were the most frequent ADRs (58.5%). Other reports referred to hepatobiliary (9.7%), nervous system (6.5%), reproductive system (5.1%), gastrointestinal (3.4%), psychiatric (2.8%), and blood (1.4%) disorders. Drug interactions and intentional overdose accounted only for 3.1% of cases each.

Dermatological disorders and acute hypersensitivity reactions

Dermatological disorders or acute hypersensitivity reactions ($n = 206$) mostly consisted of mild to moderate toxidermia ($n = 144$, 41.1%) with a median onset of nine treatment days (range 7 h to 1 year). They resulted in hospitalization in 30% of these cases. Moderate blood eosinophilia was noticed in three cases only. Complete recovery or a significant improvement of cutaneous lesions was observed in all cases with documented follow-up (outcome unknown in 28 cases). Skin tests performed in 11 patients were positive for etifoxine in only one case. However, recurrence of toxidermia was observed in six of nine patients who were re-exposed to etifoxine including one with negative skin tests. Overall, based on the time to onset of the ADR and the presence of concomitant drug(s), etifoxine was considered to be the only suspected drug in 86 (59.7%) of these cases.

Severe cutaneous reactions were reported in 25 (7.1%) patients, but one case of reversible toxic epidermal necrolysis with sequelae was poorly documented and more probably related to concomitant flurbiprofen exposure. The other cases consisted of five cases of possible

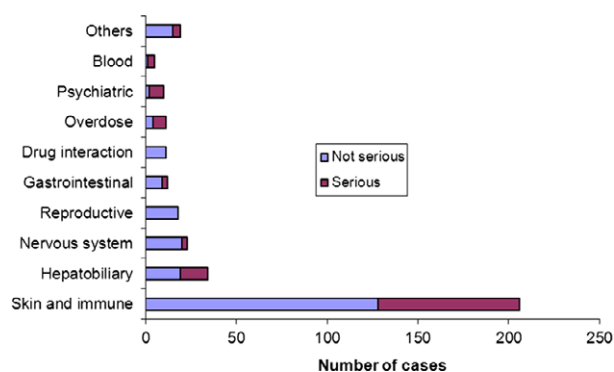


Figure 2 Distribution of etifoxine ADRs according to system organ class.

($n = 2$) or probable ($n = 3$) drug reaction with eosinophilia and systemic symptoms (DRESS) according to the Regiscar scoring [7], five cases of Stevens–Johnson syndrome (SJS), 10 cases of erythema multiforme, three cases of erythroderma, and one case of fixed pigmented erythema. In these patients, the median time to onset of the ADR was 10 days after etifoxine was started (range: 2–56). In two of the five cases of DRESS and in three of the five cases of SJS, etifoxine was either the only suspect drug or was reasonably considered to be the most likely cause. In one case of DRESS, skin tests were positive for both etifoxine and tetrazepam. Of the 10 cases of erythema multiforme, two were poorly documented and one was more probably attributable to an infection owing to the distal topography of the lesions. Etifoxine was the most suspected drug in three other patients, whereas four concomitantly took drugs that could also be involved. Finally, one patient exposed to etifoxine alone developed fixed pigmented erythema and three experienced erythroderma among which one had typical clinical and histopathological features with zoplicone as the only concomitantly suspected drug. Overall, the time frame of these cutaneous reactions was strongly suggestive of etifoxine involvement in all patients but one, and etifoxine was the most likely causative drug in 10. Complete or significant improvement of cutaneous lesions was observed after etifoxine discontinuation in all patients.

Other dermatological ADRs included: seven cases suggestive of reversible vasculitis (one biopsy-proven) or serum sickness-like reactions that occurred after a median treatment duration of 10 days (range: 3–28) with etifoxine as the most likely cause in four patients; five cases of photosensitivity; three cases of erythroderma; one case of pemphigus vulgaris that recurred after etifoxine rechallenge; and six cases of various and non-drug specific dermatological disorders.

Finally, acute hypersensitivity reactions were reported in 18 patients (severe in 8) with angioedema and/or urticarial rash in 14, and more severe reactions with systemic symptoms (two patients) or true anaphylactic-type shock (two patients). Although skin prick tests performed in only two patients were either negative or doubtful, etifoxine was considered to be the most likely cause in 13 patients including two who experienced recurrence of angioedema after etifoxine re-administration.

Hepatic disorders

Liver injury was reported in 34 (9.7%) patients with eight cases of asymptomatic liver test abnormalities,

one case of granulomatous hepatitis, and 25 cases of acute liver injury. Acute liver injury was hepatocellular in 16 patients (64%), mixed in 2, cholestatic in 2, and unclassifiable in 5. The time to onset of acute hepatitis after starting etifoxine (median: 24 days) was <2 months in 23 cases. Suggestive clinical symptoms were present in 15 patients. A severity criterion as defined by the presence of jaundice, hyperbilirubinaemia, or prothrombin time below 50% was found in four cases including two of the five patients who discontinued etifoxine more than 5 days (median: 13 days) after the appearance of the first symptoms suggestive of hepatitis. Liver biopsy performed in one patient who had recently started etifoxine, evidenced hepatocellular necrosis with inflammatory lesions and a predominance of eosinophils in an otherwise normal liver without fibrosis. All 24 patients with available follow-up improved or recovered normal liver function (outcome unknown in one). Etifoxine was the only suspected drug in eight patients and was associated with concomitant drugs not recognized as hepatotoxicants in eight others. According to the time to onset and the results of investigations to exclude a non-drug-related cause, the causal relationship with etifoxine was assessed to be possible in at least 16 patients.

Neurological and psychiatric disorders

The 23 reports of neurological disorders mostly consisted of headache ($n = 5$), visual disturbances ($n = 2$), sleep disorders with insomnia ($n = 2$) or somnolence ($n = 4$), and dizziness ($n = 3$). Other ADRs were reported only once each including nightmares, sleepwalking, impaired speech, tremors, severe extrapyramidal syndrome occurring 1 h after a single dose of etifoxine, and worsening of restless legs. Two severe cases of acute worsening of myasthenia gravis after a single dose of etifoxine confirmed the relevance of etifoxine contraindication in such patients.

There were 10 cases of psychiatric disorders such as increased anxiety, confusion, depressive, or suicidal behavioral disorders, but most of these patients were also concomitantly treated with an antidepressant drug. Interestingly, no cases of abuse, misuse or pharmacodependance were evidenced.

Gynecological disorders

A rather unexpected adverse effect was the occurrence of metrorrhagias in 16 young patients of whom 13 had been on oral contraception for a long time.

Metrorrhagias occurred after the first month of treatment in 11 patients. Concomitant treatment with citalopram, a selective serotonin reuptake inhibitor (SSRI) antidepressant sometimes associated with hemorrhagic disorders, was noticed in only one patient. The causal relationship with etifoxine treatment was assessed to be possible or very likely as metrorrhagias disappeared after etifoxine discontinuation in all 10 patients with follow-up and, more importantly, recurred in five after etifoxine rechallenge. According to the MAH data, two additional cases of metrorrhagias were also reported outside France.

Gastrointestinal disorders

Beside eight case reports of abdominal pain, vomiting, and dyspepsia, and one doubtful necrosis of the tongue, four women developed acute colitis reversible upon etifoxine discontinuation among whom three had biopsy-proven microscopic colitis and one subacute inflammatory lesions of the colon. Etifoxine was the only suspected drug in two patients while concomitant SSRI antidepressant treatment (sertraline and paroxetine) was associated in the two other patients. More importantly, colitis recurred after etifoxine re-administration in one previously published case [9].

Miscellaneous ADRs

Among the other ADRs of interest, we focused on etifoxine overdose and drug–drug interactions.

Eleven cases of etifoxine overdose involved young patients (mean age: 20 years) in whom the estimated ingested dose ranged from 500 to 2000 mg (median: 1000 mg, $n = 7$). Etifoxine was the suspected cause in four patients who developed drowsiness and/or dizziness and in one who experienced rhabdomyolysis with acute renal failure probably due to acute tubular necrosis (estimated ingested dose: 2000 mg).

A drug–drug interaction suggesting a possible loss of efficacy of the concomitant drug was suspected in 10 patients. Indeed, there were a decrease in International Normalized Ratio in four patients previously well stabilized by a vitamin K antagonist (fludione or acenocoumarol), four cases of oral contraceptive failure with subsequent pregnancy, one case of increased thyroid-stimulating hormone (TSH) plasma levels 3 months after etifoxine initiation with subsequent normalization after etifoxine discontinuation, and finally methadone withdrawal symptoms within 12 h after a single dose of etifoxine in the last patient.

DISCUSSION

The present study highlights several new ADRs probably due to etifoxine exposure and not previously listed in etifoxine summary of the product characteristics (SPC), namely severe cutaneous reactions, liver injury, colitis, and metrorrhagias.

The majority of dermatological ADRs consisted of benign eruption with etifoxine as the only suspected drug in more than one half of patients. The causal relationship with etifoxine exposure was even more convincingly strengthened by toxidermia recurrence after etifoxine rechallenge in six of nine patients. More importantly, etifoxine was strongly suspected to be the most likely causative drug in 10 of 24 (42%) cases of severe or specific toxidermia (two cases of DRESS, three cases of Stevens–Johnson syndrome, three cases of erythema multiforme, one case of fixed pigmented erythema, and one case of severe erythroderma) with a time frame of reaction onset highly suggestive of etifoxine involvement (median: 10 days). Although these ADRs were rare, their severity should be borne in mind and etifoxine immediately withdrawn when the first symptoms appear. These cases of severe toxidermia look like those observed with tetrazepam, a benzodiazepine used as myorelaxant. This molecule has been recently withdrawn because of serious cutaneous ADRs included severe toxidermia such as DRESS syndrome, Stevens–Johnson syndrome, and toxic epidermal necrolysis. The chemical structures of tetrazepam and etifoxine are definitely different even if their basic chemical formulas are very closed to each other. The hypothesis of a structural relationship as the cause of this cutaneous tropism appears to be rejected. Indeed, the only common part between these two molecules is a benzene ring substituted in position seven by chloride. This benzene ring system is common to the benzodiazepines, which are not affected by this predominance of cutaneous side effects.

Etifoxine-induced vasculitis should also be considered in any patient developing purpuric lesions within 15 days of etifoxine treatment. Our survey also confirms that etifoxine can be associated with acute hypersensitivity reactions including severe anaphylaxis in some patients.

We previously reported a detailed analysis of 18 cases of acute hepatitis with a cytolytic or mixed biological pattern of liver injury [4]. The present survey includes 11 additional cases of acute hepatitis and confirms our previous findings. Evidence supporting

etifoxine causative role includes the uniformity of the liver damage (64% of cytolytic hepatitis in case of acute liver injury), a suggestive time to onset after starting etifoxine (≤ 2 months in 92% of cases), the lack of any association with known hepatotoxicants in 68% of cases, the exclusion of other non-drug-related common causes of hepatitis (viral hepatitis or biliary tract abnormalities) in most patients, and a favorable outcome after etifoxine discontinuation in all patients with available follow-up. Overall, the causal relationship was considered to be plausible in 64% of patients who developed acute liver injury [6]. The mechanism of etifoxine hepatotoxicity remains unknown. The lack of clear clinical or biological signs of hypersensitivity supports an idiosyncratic rather than an immune-allergic mechanism.

This study also highlights unexpected cases of reversible metrorrhagias within the first month of treatment. As metrorrhagias disappeared after etifoxine discontinuation in all patients with follow-up and recurred in five after etifoxine rechallenge, the relationship appears to be quite definite. At the present time, no clear explanation can be provided to explain this ADR, and, to the best of our knowledge, etifoxine does not exert any effect on blood coagulation. Because most affected patients were also on oral contraception, a drug–drug interaction with oral contraceptives cannot be ruled out. This hypothesis is strengthened by 11 cases of suspected drug–drug interactions with possible loss of efficacy of vitamin K antagonists, oral contraceptives, levothyroxine, and methadone. However, no data indicating a possible involvement of etifoxine in drug interaction were found in the literature. Therefore, this mechanism needs to be confirmed by further investigations.

Finally, etifoxine-associated neuropsychiatric symptoms were those expected from the pharmacological effects of etifoxine, with no specific signal identified. Interestingly, there were no cases of abuse, misuse, or pharmacodependance in our survey.

Data from VigiBase™, the WHO global ICSRs database, were extracted and analyzed to complete this survey [10]. Only 17 cases have been reported with etifoxine. With the exception of two cases of suicide attempt, all these cases were considered as non-serious. Regarding dermatological ADRs, four cases were reported benign eruption only, consisting of acute urticaria, hypersensitivity, eruption, and rash maculopapular. No case of severe toxidermia has been

reported in other countries and no specific signal was identified from VigiBase.

Underreporting is a major limitation of the present survey, which is common to any study using a pharmacovigilance database [11] and thus makes impossible any assessment of the actual frequency of analyzed ADRs. However, underreporting of serious ADRs is of lower magnitude as compared with all ADRs globally [12]. In addition, careful documentation of the majority of cases included in this survey ensured an in-depth analysis of ADRs and therefore an accurate causal relationship assessment. Finally, spontaneous reporting is recognized to be highly valuable to detect new or very rare ADRs after drug approval [13].

Although etifoxine has been approved in France for more than 30 years, the safety profile is probably less favorable than currently anticipated. Spontaneous notifications helped detect new and potentially severe ADRs, in particular acute cytolytic hepatitis and severe toxidermia. However, as these ADRs were very rare, and etifoxine is mostly used as an alternative to benzodiazepines without any identified case of abuse or pharmacodependance in this survey, etifoxine risk–benefit ratio is still considered to be positive by the French health authorities. The release of an updated SPC taking into account these newly identified ADRs has been performed very recently and was based on the present survey.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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