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Hepatic Events Associated with Atomoxetine Treatment for Attention-Deficit Hyperactivity Disorder

Mark E. Bangs, *Ling Jin*, *Shuyu Zhang*, *Durisala Desaiah*, *Albert J. Allen*, *Holly A. Read*, *Arie Regev* and *Joachim F. Wernicke*

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, USA

Abstract

Objective: This study describes and assesses potential hepatobiliary events related to atomoxetine therapy, as reported in clinical trials and as spontaneous adverse event reports post-launch in 2002.

Methods: Case reports that contained potential hepatobiliary events were identified by a computerized search of the Eli Lilly and Company atomoxetine spontaneous adverse events and clinical trials databases. All cases were reviewed by at least two company physicians, one with expertise in hepatology, to determine the relevance of the information in respect of potential liver toxicity.

Results: Of 7961 paediatric and adult patients treated with atomoxetine in clinical trials, 41 were identified as having hepatobiliary events requiring additional analysis. Most of these events were mild increases in ALT and AST levels. None of these cases met Hy's rule criteria or progressed to liver failure. During the 4 years after market launch, 351 spontaneous reports of adverse events were related to the liver, of which 69 had other explanations unrelated to atomoxetine. Of the remaining 282 cases, 133 contained possible confounding factors (and were deemed to be possibly related), 146 presented too little information to assess, and three suggested atomoxetine as a probable cause of liver injuries. One of the three had a positive rechallenge. All three patients recovered after discontinuation of the drug.

Conclusions: Since the launch of atomoxetine therapy, three spontaneously reported cases of reversible drug-induced liver injury were deemed probably related to it. Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted.

Background

Drugs have been estimated to cause >50% of acute liver failure cases in the US.[1] Drug-induced liver injury (DILI) is a potential complication of nearly every medication, because the liver is central to the metabolism of virtually all drugs and foreign substances. Consequently, drugs are monitored for hepatotoxic potential during development, and monitoring continues once marketing approval is received. Two broad categories of liver injury from drugs are recognized: dose-dependent injury and injury that occurs from idiosyncratic factors. Dose-dependent injuries are usually identified during early drug development. This type of liver injury is

often characterized by uniformity and predictability, in terms of the time the injury appears after dosing begins and the particular 'target' liver cell(s) destroyed. Idiosyncratic DILI can present in any histopathological form and may not follow a single pattern of latency.[2] Idiosyncratic DILI is unpredictable among drug recipients and toxicity does not appear to be dose related. Because it is very rare (fewer than 1 in 10 000 patients), dose relationships may not be apparent, simply because not enough cases or different doses are available for assessment.[3] All these features of idiosyncratic DILI result in difficult and often contentious attempts to assess the cause of liver injury associated with the use of a new drug. Idiosyncratic DILI has always been a diagnosis of exclusion; direct evidence implicating the drug is usually absent. The purpose of this study was to review the data on potential hepatobiliary events associated with atomoxetine therapy in clinical trials and post-launch. This article also describes four cases of voluntarily reported liver injury that were deemed possibly or probably related to atomoxetine, to illustrate some of the difficulties inherent in post-marketing safety surveillance for rare events and accurate communication of the risk of these events.

Atomoxetine, a selective noradrenergic re-uptake inhibitor,[4-6] was approved for the treatment of attention-deficit hyperactivity disorder (ADHD) by the US FDA in November 2002. Repeat-dose oral toxicity studies of atomoxetine carried out by Eli Lilly and Company in rats, mice and dogs did not show any major organ toxicity.[7] Hepatotoxicity was not observed in either rats or dogs given atomoxetine intravenously.[7] The primary metabolic pathway for atomoxetine is via the hepatic cytochrome P450 (CYP) 2D6 pathway.[8] Clinical studies involving over 4000 children, adolescents and adults were completed for the New Drug Application (NDA), including CYP2D6 genotyping, to establish efficacy and safety for all possible patients.[7,9] No differences in safety measures, including the type and severity of adverse events, were apparent between the patients by CYP2D6 genotype status.[7,9] Since the NDA submission, there have been additional clinical trial patients enrolled and new studies started.[10-18] Several of the early studies have been published.[19-24] Following the approval of atomoxetine in the US, Eli Lilly and Company has performed continuous monitoring of spontaneous reports of adverse events associated with atomoxetine use. Particular attention and extensive follow-up have been given to certain targeted events, such as liver injury. Reports of three cases of significant liver injury following atomoxetine use were published recently by Lim et al.[25] and Stojanovski et al.[26]

Methods

Clinical Studies

Considering that previous reviews of Eli Lilly and Company's clinical trials data had shown that hepatic events associated with atomoxetine were uncommon,[27-29] the databases on all paediatric and adult patients exposed to atomoxetine (Strattera®[1]) in ADHD clinical trials were searched. This provided substantially more exposure time than the placebo-controlled trials. Potential hepatic events were identified using a two-part automated search strategy of the atomoxetine clinical trials databases, which included 45 studies involving 7961 paediatric and adult patients. The first part of the search used seven predefined abnormal laboratory criteria shown in table I, including key markers of liver injury such as ALT, AST, alkaline phosphatase (ALP) and total bilirubin (TBILI) to identify patients with potential DILI. The second part of the search used a computerized text-string search program to review investigators' actual descriptions of trial adverse events and the preferred terms used to code those events from the Medical Dictionary for Regulatory Activities (MedDRA). This was to ensure that all potential liver injury cases would be detected. Text-strings were generated from liver-related MedDRA terms (Version 7.0). Examples of

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Laboratory criteria used to identify relevant patient cases from clinical studies

Item	Criterion
i	ALT ≥3 × ULN and TBILI ≥1.5 × ULN
ii	TBILI ≥1.5 × ULN and ALT and AST normal values
iii	ALT ≥3 × ULN and ALP >2 × ULN
iv	ALT ≥3 × ULN and ALP >2 × ULN and TBILI ≥1.5 × ULN
v	ALT ≥2 × ULN and ALT/ALP ratio ≥5 (hepatocellular)
vi	ALP >2 × the ULN and ALT/ALP ratio <2 (cholestatic)
vii	ALT ≥2 × ULN and ALP ≥2 × ULN and ALT/ALP ratio >2 and <5 (mixed)

ALP = alkaline phosphatase; **TBILI** = total bilirubin; **ULN** = upper limit of normal.

the text-stings are 'liver', 'hepato', 'hepati', 'biliar', 'chol' and 'jaundice'.

Additional analyses were performed using laboratory data obtained during 14 paediatric and two adult placebo-controlled clinical ADHD trials. The paediatric trials involved 1288 patients on atomoxetine and 755 patients on placebo. There were 261 adult patients treated with atomoxetine and 248 taking placebo in the two adult trials. The percentages of patients encountering treatment-emergent high values of a hepatic enzyme (ALT, AST, γ-glutamyltransferase [GGT] and ALP) or TBILI during the trial were compared between the two treatments. For these analyses, a treatment-emergent high value was defined as a change from a value less than or equal to the upper limit of normal (ULN) at baseline to a value greater than the ULN at any post-baseline assessment (post-baseline being defined as the phase when patients were taking the study drug). The significance of the overall differences was assessed using the Cochran-Mantel-Haenszel general association test stratified by study group. Change from baseline to maximum was computed for all hepatic enzymes (ALT, AST, ALP and GGT) and TBILI using a last-observation-carried-forward approach. The mean change from baseline comparisons between treatments was assessed using an analysis of variance. The model included main effects for treatment, protocol and treatment-by-protocol interaction. The significance of the difference between groups was based on raw data for laboratory values. All tests employed a 0.05 statistical significance level.

Spontaneous Reports

The atomoxetine post-marketing spontaneous reports database was subjected to a computerized search similar to that described above, to identify hepatobiliary events reported during a 4-year period between 26 November 2002 and 26 November 2006. As before, a text-string search was employed using MedDRA high-level group terms and preferred terms related to hepatic events and laboratory abnormalities.

Physician Review

Two company physicians (including one hepatologist) trained in the review of drug toxicity reviewed each case independently, and a third physician reviewed and adjudicated the cases where disagreements arose. Two cases presented in this paper were also reviewed by external hepatologists. Events deemed not to be hepatobiliary injury were excluded from further review. 'Possible liver injury' was defined as any enzyme increase >2 × ULN for ALT, AST or ALP, or an increase >1.5 × ULN for TBILI, values derived from the 2000 FDA White Paper.[30] Clinical trial and spontaneous cases were also reviewed as to whether they met the criteria for Hy's rule (ALT ≥3 × ULN and TBILI >2 × ULN), an important marker of potential mortality.[31]

All cases identified from the two-part automated search of the clinical trials database described earlier were reviewed and categorized for causality using an algorithm based on diagnostic criteria and potential aetiological confounding factors. Our causality assessment was based on the criteria outlined in the Roussel Uclaf Causality Assessment Method (RUCAM).[32] This method provides a uniform assessment of the pattern of injury, time of onset from initiation of drug therapy, course of illness after the suspect drug was stopped, presence of risk factors including concomitant medications and evaluation of other possible causes of liver injury. Because of incomplete data in many of the spontaneously reported cases, hepatology expert opinion was used as a complementary tool where the RUCAM could not be applied fully. Each one of the spontaneously reported cases was classified for causality into one

of four categories: (i) unlikely to be related to atomoxetine; (ii) possibly related; (iii) probably related; or (iv) indeterminate (insufficient information).

Results

Clinical Trials

Data included in the analyses are from 45 clinical trials in which data were locked on or before 1 March 2006, comprising 7961 patients. The text-string and laboratory searches yielded a total of 226 potential DILI cases. Physician review eliminated 185 of the 226 cases, because they were determined to be unrelated to atomoxetine use or not a significant hepatic event according to the 2000 FDA White Paper (enzyme elevations ≤2 × ULN or TBILI elevations ≤1.5 × ULN). Based on the causality assessment described above, 41 cases among 7961 treated patients were deemed to be possibly related to atomoxetine. Of these 41 patients, none met Hy's rule criteria (ALT ≥3 × ULN and TBILI >2 × ULN) or progressed to liver failure. The proportion of male patients was 83% (n = 34), which is similar to the sex distribution of patients with ADHD in the general population.

Eighteen patients showed a mild to moderate increase in TBILI in the absence of other significant biomarker abnormalities, consistent with Gilbert's syndrome. Of the remaining 23 patients, nine had elevated ALT up to 5 × ULN; one patient presented with an ALT increase 13 × ULN associated with viral nasopharyngitis and paracetamol use; two patients likely experienced muscle injury (one of whom had an elevated AST along with creatine phosphokinase [CPK] 33 × ULN, and another had elevated ALT 4 × ULN, AST 5.5 × ULN and CPK 6 × ULN); three patients had increased ALP that was present before atomoxetine treatment; and eight patients had a mild increase of both TBILI and ALP that may have been indicative of mild cholestatic injury. This analysis was consistent with the findings at the time of the marketing approval of atomoxetine. There was no apparent evidence of significant liver injury associated with atomoxetine use in clinical trials.

In the 14 paediatric and 2 adult trials, the proportions of patients with treatment-emergent high values (>1 × ULN) of liver enzymes or TBILI in atomoxetine paediatric and adult placebo-controlled trials are presented in figure 1. There were no significant differences between the atomoxetine and placebo treatments in either paediatric or adult patients for treatment-emergent high values of hepatic enzyme (ALT, AST, GGT and ALP) or TBILI during the trials.

Table II and table III summarize the mean change from baseline to endpoint for hepatic laboratory values in short-term, placebo-controlled paediatric and adult studies, respectively. In placebo-controlled, ADHD clinical trials of short duration (up to 18 weeks), placebo-treated paediatric patients had increases in mean change from baseline to maximum in ALT and ALP, while AST and GGT mean values decreased. Atomoxetine-treated patients had decreases in mean change for those measures; these differences were statistically significant. Although these changes may have been statistically significant, they were small and not clinically relevant.

In placebo-controlled ADHD clinical trials of short duration (up to 6 months), placebo-treated adult patients had statistically significantly greater increases than atomoxetine-treated patients in change from baseline to maximum for TBILI.

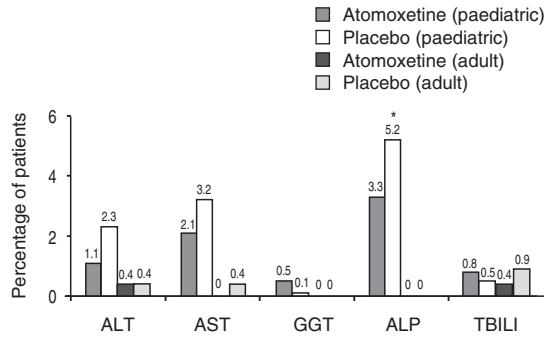

Fig. 1. Proportion of patients with treatment-emergent high values (>1 × ULN) for liver tests in placebo-controlled ADHD clinical trials. **ADHD** = attention-deficit hyperactivity disorder; **ALP** = alkaline phosphatase; **GGT** = γ-glutamyltransferase; **TBILI** = total bilirubin; **ULN** = upper limit of normal; * $p < 0.01$.

Table II. Mean change from baseline to endpoint of hepatic laboratory values in all randomized paediatric attention-deficit hyperactivity disorder (ADHD) patients

Laboratory values	Baseline mean (SD)		Endpoint change mean (SD)		p-Values
	placebo	atomoxetine	placebo	atomoxetine	
ALT (IU/L)	18.4 (9.12)	18.3 (8.54)	0.26 (9.51)	−1.79 (9.13)	<0.001
AST (IU/L)	27.7 (6.62)	27.9 (6.90)	−0.12 (5.68)	−1.00 (6.81)	0.003
ALP (IU/L)	247.9 (78.47)	244.15 (74.02)	6.29 (38.41)	−6.56 (35.52)	<0.001
GGT (IU/L)	13.2 (4.52)	13.0 (4.91)	−0.10 (2.65)	−0.39 (3.34)	0.021
TBILI (μmol/L)	6.5 (3.28)	6.6 (3.69)	0.13 (2.69)	0.27 (2.98)	0.232

ALP = alkaline phosphatase; **GGT** = γ-glutamyltransferase; **TBILI** = total bilirubin.

Atomoxetine-treated patients had statistically significantly greater increases than placebo-treated patients in mean change from baseline to maximum for ALP. Although these differences were statistically significant, the changes were small and not clinically significant.

Post-Marketing Spontaneous Adverse Event Reports

The search in the atomoxetine spontaneously reported adverse event database identified a total of 351 spontaneous case reports as potential liver injury in temporal association with atomoxetine. The calculated reporting rate of liver injury events in the atomoxetine spontaneous adverse event database was <0.01% (i.e. 351 cases among 4 328 000 patients exposed to atomoxetine in the period examined). Of these 351 cases, 69 were categorized as being unlikely to be related to atomoxetine use, because of other clear contributing factors for liver injury such as Gilbert's syndrome, acute viral hepatitis or negative rechallenge of atomoxetine. The aetiology of liver injury could not be categorized in another 146 cases, because of a lack of information for evaluation. Finally, 136 of the 351 cases were categorized as being possibly (133 cases) or probably (three cases) related to atomoxetine treatment. Within this group of 136 cases, there were 13 with AST or ALT ≥500 U/L (≥10 × ULN), five cases that met criteria for Hy's rule and two cases of liver failure. Three of the cases that were categorized as probably related to atomoxetine treatment had fairly complete negative investigations for other causes. The clinical details of these three cases are described below and laboratory data are provided in table IV.

Case Reports

Case 1

The patient in this unpublished report was a Caucasian male in his mid-teens who had no history of liver disease, autoimmune disease, recent surgeries, recent travel, or alcohol or drug use. The patient was also taking sertraline for anxiety and depression. He had been receiving atomoxetine 40 mg twice daily for treatment of ADHD for approximately 3–4 months when he began to experience lethargy and abdominal pain. Atomoxetine and sertraline were discontinued. Peak laboratory values

Table III. Mean change from baseline to endpoint of hepatic laboratory values in all randomized adult attention-deficit hyperactivity disorder (ADHD) patients

Laboratory values	Baseline mean (SD)		Endpoint change mean (SD)		p-Values
	placebo	atomoxetine	placebo	atomoxetine	
ALT (IU/L)	28.2 (15.06)	25.34 (13.25)	0.04 (12.98)	0.24 (9.75)	0.703
AST (IU/L)	24.2 (8.27)	23.5 (6.56)	0.71 (9.03)	0.10 (6.00)	0.491
ALP (IU/L)	70.9 (19.11)	70.2 (18.93)	−2.00 (9.18)	2.98 (9.74)	<0.001
GGT (IU/L)	24.4 (15.85)	23.1 (17.10)	0.42 (9.09)	1.15 (9.47)	0.337
TBILI (μmol/L)	8.4 (4.35)	8.6 (4.53)	0.14 (3.37)	−0.52 (3.46)	0.036

ALP = alkaline phosphatase; **GGT** = γ-glutamyltransferase; **TBILI** = total bilirubin.

Table IV. Laboratory data of the three cases

Test performed	Case 1 (ULN)	Case 2 (ULN)	Case 3 (ULN)
AST initial/peak (IU/L)	834/2093 (60)	2999/3505 (45)	5156/6619 (45)
ALT initial/peak (IU/L)	1236/1640 (45)	3264/3264 (50)	5182/5182 (65)
TBILI initial/peak (mg/dL)	1.0/18.0 (1.2)	9.1/9.8 (1.0)	10.8/14.3 (1.0)
ALP initial/peak (IU/L)	282/446 (500)	231/363 (397)	528 (150)
ANA, anti-LKM	Negative (two negatives)	1 : 160 (<1 : 40) <1 : 20 (<1 : 20)	Negative
AMA	Negative	NR	NR
SMA	NR	1 : 20 (<1 : 20)	Negative
Viral titre A, B, C	Negative	Negative	Negative
EBV adenovirus	NR	Negative	Negative
CMV IgM	Negative	Negative	Negative
α-1 antitrypsin (mg/dL)	NR	277 (215)	
Serum ceruloplasmin (mg/dL)	Normal	49.2 (14–57)	Negative

ALP = alkaline phosphatase; **AMA** = antimitochondrial antibody; **ANA** = antinuclear antibody; **CMV** = cytomegalovirus; **EBV** = Epstein-Barr virus; **IgM** = immunoglobulin M; **LKM** = liver-kidney-microsomal antibody; **NR** = not reported; **SMA** = smooth muscle antibody; **TBILI** = total bilirubin; **TIBC** = total iron-binding capacity; **ULN** = upper limit of normal.

were detected the day after atomoxetine and sertraline were discontinued, as ALT was elevated to 33 × ULN, AST to 15 × ULN and TBILI to 1.5 × ULN. The liver enzyme profile at different timepoints is shown in figure 2. Other laboratory values are provided in table IV. Tests for viral hepatitis, smooth muscle and antinuclear antibodies (ANAs) were all negative. Abnormal liver enzymes returned to normal within 2 months. The patient was rechallenged with atomoxetine 40 mg/day, and within approximately 5 weeks, aminotransferases and bilirubin were elevated. Atomoxetine was discontinued. Hepatic enzymes peaked at ALT 37 × ULN, AST 35 × ULN and TBILI 16 × ULN (with primarily increase of direct bilirubin) after the rechallenge. Liver biopsy showed hepatitis with focal hepatocellular necrosis. Again, no other specific cause for the liver injury could be identified. Approximately 2 months after the rechallenge, a second liver biopsy was carried out, which showed hepatitis with cholestasis

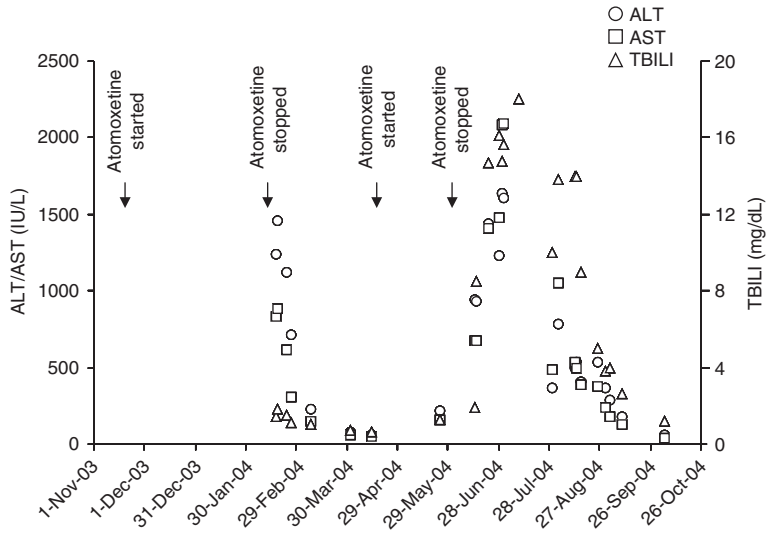

Fig. 2. Liver biomarker results over time for case 1. **TBILI** = total bilirubin.

and primarily lymphocytic inflammatory infiltrate. Abnormal laboratory values gradually returned to normal over a period of approximately 4.5 months. About 10 months after the rechallenge, liver enzyme tests showed normal results, and the patient eventually made a full recovery.

Case 2

The patient, a female in early adolescence, is one of two detailed in a paper published by Lim et al.[25] (the other patient reported in this paper is not discussed here as the liver injury was not judged to be related to atomoxetine). After taking atomoxetine 40 mg/day (1.0 mg/kg/day) for nearly 1 year, she was admitted to hospital with jaundice, abdominal pain, diarrhoea and vomiting. Her physical examination was remarkable for conjunctival icterus and right upper quadrant tenderness, but there was no hepatosplenomegaly. Her initial laboratory values revealed ALT 65 × ULN, AST 67 × ULN, TBILI 9.1 × ULN and normal ALP. An extensive work-up was negative for infectious, metabolic or autoimmune causes, although her ANA titre was weakly positive at 1 : 160 (normal <1 : 40). Other laboratory values are provided in table IV. Liver biopsy showed intact lobular architecture within focal thin fibrous bridging. Portal areas contained moderate mixed inflammatory infiltrate, mainly lymphoid in nature with some eosinophils, normal interlobular bile ducts and normal central veins. The patient stopped taking atomoxetine and over the next 4 weeks her symptoms and abnormal laboratory results gradually improved with no further intervention.[25] Eli Lilly and Company received this case report in 2005 and now considers this case as being probably related to atomoxetine use, because the patient was known to have taken atomoxetine and did not have other significant confounding factors.

Case 3

The patient, a female child, is detailed in a published case report by Stojanovski et al.[26] After taking atomoxetine 25 mg/day (1.03 mg/kg/day) for 37 days, she presented to her primary care physician with a 2-day history of emesis. Laboratory values revealed ALT 80 × ULN, AST 115 × ULN, TBILI 10.8 × ULN and ALP 3.5 × ULN. Upon admission to the hospital, her physical examination was remarkable for jaundice and hepatomegaly. An extensive work-up was negative for infectious, autoimmune or metabolic causes. Laboratory values are provided in table IV. A liver biopsy obtained on the eighth day of hospitalization displayed mixed portal inflammation composed of lymphocytes, neutrophils and a few eosinophils, extending through the lobule with moderate piecemeal necrosis. She improved gradually and was discharged after 13 days in the hospital.[26] Eli Lilly and Company received this case report in 2005 and classified it as possibly associated with atomoxetine treatment in a previous review. With more detailed information provided in the published case report, Eli Lilly and Company now considers this event as being probably related to atomoxetine use, because the patient was known to have taken atomoxetine (25 mg/day for 37 days) and did not have other significant confounding factors.

Case 4 (Now Reclassified as Autoimmune Hepatitis Possibly Related to Atomoxetine)

In addition to the three cases described above, a fourth unpublished case was initially categorized as being probably related to atomoxetine treatment. Subsequent information resulted in a reclassification to an autoimmune hepatitis possibly related to atomoxetine.

The patient, a Caucasian female in her early 30s, had a history of rare alcohol use and no known preexisting medical conditions. She was receiving atomoxetine for ADHD at a dosage titrated from 18 to 40 mg/day. She had been on buproprion 300 mg/day when atomoxetine was started. The buproprion dose was decreased to 150 mg/day after about 1 month and then discontinued 2 months after atomoxetine initiation. Approximately 3 weeks later, she went to the emergency room with symptoms of nausea and jaundice. Atomoxetine was discontinued. Liver enzymes peaked at approximately ALT 36 × ULN, AST 37 × ULN and TBILI 16 × ULN (primary increase of indirect bilirubin) and ALP 2 ×

ULN. The liver needle biopsy showed acute hepatitis with cholestasis and no fibrosis. Upon treatment with prednisone, liver enzymes returned to normal about 4 months after atomoxetine was discontinued. Several months later, the patient experienced a second episode of hepatitis with an ALT elevation to 23 × ULN without rechallenge of atomoxetine. Prednisone treatment again resulted in recovery. Although the usual ANA and anti-liver-kidney microsomal antibodies were negative, the reporter reconsidered the diagnosis to be autoimmune hepatitis, which was treated with oral azathioprine. That the hepatitis recurred after atomoxetine had been discontinued made it seem less likely that the first episode was the result of atomoxetine use, although there is the possibility that atomoxetine could have triggered the first autoimmune response.

Discussion

The preclinical testing of atomoxetine in rats, mice and dogs carried out by Eli Lilly and Company did not identify any clinical or biochemical liver toxicity.[7] Before its launch in 2002, atomoxetine had been administered to over 4000 children, adolescents and adults. There was no significant evidence of liver toxicity in any of these clinical trials.[10,19-24] In placebo-controlled studies, there was no difference between atomoxetine and placebo in the proportion of patients with treatment-emergent abnormal liver function tests in paediatric or adult patients with normal baseline values. Following 2 years of post-marketing exposure, two cases of reversible hepatocellular liver injury were reported by different healthcare professionals (discussed here as case 1 and case 4), suggesting that drug-related liver injury had occurred. The estimated global exposure to atomoxetine was about 2.2 million patients at that time. In both patients, the abnormality in hepatic biochemical tests resolved when atomoxetine was stopped. One case of hepatitis recurred following rechallenge with atomoxetine, supporting a casual relationship. In the other patient, although she had received corticosteroid therapy during her recovery, corticosteroids were not believed to have contributed to the resolution of her illness at the time these cases were discussed with the FDA. These two cases were deemed to provide sufficient evidence of an increased risk of liver toxicity to warrant a label change for atomoxetine in 2004. The emboldened warning in the US package insert was accompanied by a "Dear healthcare professional" letter and communications to other regulatory bodies around the world. The FDA and Eli Lilly and Company agreed that baseline testing and monitoring of liver transaminases were unlikely to provide protection against additional cases of hepatitis.

Although one of the cases that prompted the change in the atomoxetine US package insert was subsequently reclassified as being only possibly related to atomoxetine treatment, because of a second episode of hepatitis after atomoxetine had been discontinued (case 4), two other cases of liver injury reported in the literature were deemed to be probably related to atomoxetine treatment (cases 2[25] and 3[26]). Thus, to date, Eli Lilly and Company is aware of three cases of liver injury probably related to atomoxetine use having been reported. Considering the now extensive exposure to atomoxetine, >4 million patients after 4 years, these reactions are very rare and fit the pattern of an idiosyncratic drug reaction.

The calculated reporting rate of liver injury events, regardless of aetiology, in the atomoxetine spontaneous adverse events database was <0.01% (i.e. 351 cases among 4 328 000 patients exposed to atomoxetine in the first 4 years of post-marketing experience). The actual incidence of liver events in the atomoxetine-treated population cannot be determined from these data, since under-reporting of events is a well known limitation of voluntary reporting systems. Very severe events suspected of possibly being a drug reaction, however, would be expected to be more likely to be reported, but even severe DILI has been shown to be under-reported.[33]

Reporting rates calculated as reports per 100 000 person-years provide figures that can be compared more appropriately with incidence rates adjusted for duration of exposure, as reported in the literature, although even these are not identical measures. The reporting rate calculated using the overall number of

liver injury cases reported to Eli Lilly and Company was 23.7 per 100 000 person-years. Because there is likely to be some level of under-reporting, we have also presented rates calculated using multipliers of five and ten: 118.5 per 100 000 person-years and 237.0 per 100 000 person-years, respectively. The range of estimates of liver injury background rates varies widely, from a low of 0.7 per 100 000 person-years for DILI[34] to 164.9 per 100 000 person-years for all causes of liver injury.[35] The reporting rates for liver injury with atomoxetine, estimated using actual number of reports as well as using a multiplier of five, fall within the range of estimates of the background rate. The reporting rate, using a multiplier of ten, exceeded, but was of the same order of magnitude as, the background rate.

The limitations of estimating reporting rates and selection of multipliers must be considered in interpreting the results of this analysis. Reporting rates should not be interpreted as estimates of the true incidence of an adverse event among patients taking a particular drug, but rather as indicators of the approximate range of adverse event rates among individuals taking that drug. Taken together, and with these caveats in mind, these data suggest that the incidence of liver injury in patients taking atomoxetine appears to be within the background rate for the general population, even when considering under-reporting.

In conclusion, three spontaneously reported cases of reversible hepatitis have been identified in association with atomoxetine therapy during the 4-year post-marketing period when atomoxetine exposure had reached about 4.3 million patients. These cases are consistent with the pattern of an idiosyncratic drug reaction. Atomoxetine therapy should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted. Laboratory testing to determine liver enzyme levels should be carried out at the first sign or symptom of liver injury (e.g. pruritus, dark urine, jaundice, right upper quadrant tenderness or unexplained 'flu-like' symptoms).[36]

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Correspondence: *Mark E. Bangs*, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA.
E-mail: bangsme@lilly.com