



Sibutramine

Updated: January 2, 2014.

OVERVIEW

Introduction

Sibutramine is a serotonin and norepinephrine reuptake inhibitor which has been used for short- and long-term therapy of obesity, but which was withdrawn from use in 2010 because of increase risk of cardiovascular events. In large clinical trials, sibutramine therapy was not associated with serum enzyme elevations, and it has only rarely been implicated in cases of clinically apparent, acute liver injury.

Background

Sibutramine (si bue' tra meen) is a beta-phenylethylamine that inhibits the synaptic reuptake of both serotonin and norepinephrine. Developed initially as an antidepressant, it had little effect on depression, but its use was associated with weight loss that appeared to be due to decreased appetite and reduced caloric intake. Sibutramine was approved for use as therapy of obesity in the United States in 1997 and was widely prescribed until it was withdrawn in 2010 because of studies demonstrating an increased risk of myocardial infarction and stroke with its use. Sibutramine was previously available as capsules of 5, 10 and 15 mg under the trade name Meridia. The recommended dose was 10 mg once daily, with adjustment up to 15 mg daily or down to 5 mg daily based upon clinical effect and tolerance. Common side effects included dry mouth, headache, insomnia, constipation, nausea and increased blood pressure and heart rate. While no longer available commercially, sibutramine has been found as a contaminant in some weight loss products available over-the-counter or via the internet.

Hepatotoxicity

Sibutramine has not been linked to an increased rate of serum enzyme elevations during therapy, but the results of serum ALT monitoring have been reported only rarely. Despite its long term availability, only a single case report of acute liver injury attributed to sibutramine has been published. The time to onset was 2 weeks and the pattern of liver enzyme elevation was cholestatic. The liver injury was anicteric and self-limited in course. Immunoallergic and autoimmune features were absent. There have been no reports of acute liver failure or chronic liver injury attributed to sibutramine.

Mechanism of Injury

The mechanism by which sibutramine might cause liver injury is not known. Sibutramine undergoes extensive hepatic metabolism, primarily by the cytochrome P450 system (CYP 3A4) to its active metabolite which may be further metabolized and conjugated in the liver. Thus, a possible mode of liver injury is production of a toxic intermediate.

Drug Class: [Weight Loss Agents](#)

CASE REPORT

Case 1. Anicteric acute liver injury attributed to sibutramine use.

[Modified from: Chounta A, Tsiodras S, Zouridakis S, Doumas M, Giamarellou H. Sibutramine use associated with reversible hepatotoxicity. *Ann Intern Med* 2005; 143: 763-4. [PubMed Citation](#)]

A 47 year old obese woman with type 2 diabetes developed fatigue, weakness and pruritus followed by dark urine and jaundice arising 2 weeks after starting sibutramine (10 mg daily). She had no history of liver disease, alcohol abuse or risk factors for viral hepatitis. Her only other medication was insulin. She drank herbal tea. Sibutramine was taken for a total of 20 days and stopped once liver injury was identified. Laboratory testing showed normal serum bilirubin levels, but moderate elevations in ALT (222 U/L), AST (98 U/L) and alkaline phosphatase (763 U/L) (Table). Serological tests for viral hepatitis were negative as were routine autoantibodies. Abdominal ultrasound, computerized tomography and magnetic resonance imaging showed a small gallbladder polyp, but no evidence of liver enlargement or biliary obstruction. A liver biopsy showed a mixed inflammatory infiltrate without fibrosis or cholestasis. Upon stopping the medication, she began to improve clinically and laboratory tests fell rapidly and were normal when tested 8 months later.

Key Points

Medication:	Sibutramine (10 mg daily)
Pattern:	Cholestatic (R=0.8)
Severity:	1+ (enzyme elevations without jaundice)
Latency:	2 weeks to symptoms, 3 weeks to jaundice
Recovery:	2-3 months
Other medications:	Insulin, herbal tea

Laboratory Values

Time After Starting	Weeks After Stopping	ALT (U/L)	Alk P (U/L)	GGT (U/L)	Other
3 weeks	0	222	763	925	Sibutramine stopped
9 weeks	6 weeks	41	179	228	Asymptomatic
5 months	4 months	29	154	60	
7 months	6 months	70	139	92	
9 months	8 months	33	75	30	
Normal Values		<42	<115	<50	

Comment

The timing of onset of liver test abnormalities, the cholestatic pattern of enzyme elevations and the liver histology were all compatible with drug induced liver injury, and the only apparent candidate was sibutramine. Normalization of the alkaline phosphatase and GGT were delayed, but this is common after cholestatic liver injury. The lack of bilirubin elevation indicates that the injury, while symptomatic, was mild.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Sibutramine – Meridia®

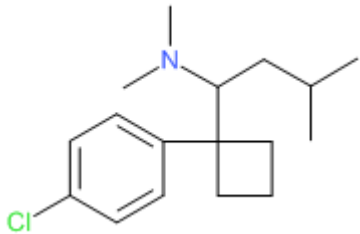
DRUG CLASS

Weight Loss Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Sibutramine	106650-56-0	C ₁₇ H ₂₆ ClN	

ANNOTATED BIBLIOGRAPHY

References updated: 02 January 2014

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 483-91.

(Expert review of hepatotoxicity published in 1999; sibutramine is not mentioned).

Westfall TC, Westfall DP. Adrenergic agonists and antagonists. In, Brunton LL, Chabner BA, Knollman BC. Goodman & Gilman's The pharmacological basis of therapeutics, 12th ed. New York: McGraw-Hill, 2011. p. 277-333.

(Textbook of pharmacology and therapeutics).

Luque CA, Rey JA. Sibutramine: a serotonin-norepinephrine reuptake-inhibitor for the treatment of obesity. Ann Pharmacother 1999; 33: 968-78. PubMed PMID: 10492502.

(Review of chemistry, pharmacology, metabolism, clinical efficacy and safety of sibutramine; no mention of hepatitis or ALT elevations in discussion of side effects).

Bray GA. A concise review on the therapeutics of obesity. Nutrition 2000; 16: 953-60. PubMed PMID: 11054601.

(Overview of the mechanism of action of anti-obesity medications and their clinical efficacy and side effects; no mention of ALT elevations or liver related adverse events).

Haddock CK, Poston WS, Dill PL, Foreyt JP, Ericsson M. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *Int J Obes Relat Metab Disord* 2002; 26: 262-73. PubMed PMID: 11850760.

(Metaanalysis of published studies of anti-obesity medications; sibutramine has been studied in 5 controlled trials published between 1991-98; no discussion of side effects).

Sabuncu T, Nazligul Y, Karaoglanoglu M, Ucar E, Kilic FB. The effects of sibutramine and orlistat on the ultrasonographic findings, insulin resistance and liver enzyme levels in obese patients with non-alcoholic steatohepatitis. *Rom J Gastroenterol* 2003; 12: 189-92. PubMed PMID: 14502318.

(Trial of 6 month course of sibutramine [n=13] vs orlistat [n=12] in 25 obese patients with nonalcoholic steatohepatitis; both agents were associated with weight loss and improvements in hepatic fat and ALT levels [79 to 32 U/L], but slight increase in Alk P [~175 to ~196 U/L]; no patient stopped therapy because of side effects).

Colman E. Anorectics on trial: a half century of federal regulation of prescription appetite suppressants. *Ann Intern Med* 2005; 143: 380-5. PubMed PMID: 6144896.

(History of the approval of medications for obesity from initial agents approved in 1947 to sibutramine in 1997; sibutramine was approved in 1997, but its long term usefulness and safety remain controversial).

Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR, Hilton L, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* 2005; 142: 532-46. PubMed PMID: 15809465.

(Systematic review of efficacy and safety of medications for obesity; sibutramine effects were evaluated in 29 published studies which showed an overall significant effect on weight loss when combined with lifestyle modification; no serious adverse events and no mention of hepatotoxicity).

Chounta A, Tsiodras S, Zouridakis S, Doumas M, Giamarellou H. Sibutramine use associated with reversible hepatotoxicity. *Ann Intern Med* 2005; 143: 763-4. PubMed PMID: 16287809.

(47 year old woman developed fatigue and pruritus 2 weeks after starting a 20 day course of sibutramine [bilirubin normal, ALT 222 U/L, Alk P 763 U/L], resolving 6-8 months after stopping: Case 1).

Bray GA. Drug Insight: appetite suppressants. *Nat Clin Pract Gastroenterol Hepatol* 2005; 2: 89-95. PubMed PMID: 16265126.

(Review of the mechanism of action and clinical efficacy of drugs that suppress appetite including sympathomimetic agents [amphetamine, phentermine, sibutramine], serotonin reuptake inhibitors [bupropion, fenfluramine, fluoxetine], GABAergic agents [topiramate, zonisamide], cannabinoid antagonists [rimonabant] and various peptides [leptin, neuropeptide Y, melanocortin-4]; no discussion of hepatotoxicity).

Ioannides-Demos LL, Proietto J, Tonkin AM, McNeil JJ. Safety of drug therapies used for weight loss and treatment of obesity. *Drug Saf* 2006; 29: 277-302. PubMed PMID: 16569079.

(Review of safety of drug therapy of obesity; the only mention of liver adverse events was "a case of reversible hepatotoxicity associated with sibutramine").

James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, Torp-Pedersen C, et al.; SCOUT Investigators. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010; 363: 905-17. PubMed PMID: 20818901.

(Controlled trial of sibutramine vs placebo for a average of 3.4 years in 10,744 overweight or obese subjects with preexisting cardiovascular conditions, found increases in pulse rate, blood pressure, and nonfatal myocardial infarction and stokes; no mention of ALT levels or hepatotoxicity).

Sibutramine (Meridia) withdrawn. *Med Lett Drugs Ther* 2010; 52 (1350): 88. PubMed PMID: 21045763.

(Announcement that sibutramine was withdrawn from the market because of concerns over cardiovascular safety in the US, Canada, Europe and Australia, but remains available in other countries).

van Hunsel F, van Grootheest K. [Adverse drug reactions of a slimming product contaminated with sibutramine]. *Ned Tijdschr Geneesk* 2011; 155: A3695. PubMed PMID: 22027464.

(Two reports of adverse events due to "Green Coffee 800", an unregistered weight loss agent that was found to be contaminated with sibutramine; one patient had serum ALT elevations).

Ozdemir B, Sahin I, Kapucu H, Celbis O, Karakoc Y, Erdogan S, Onal Y. How safe is the use of herbal weight-loss products sold over the Internet? *Hum Exp Toxicol* 2012. [Epub ahead of print] PubMed PMID: 22354083.

(Testing of 9 weight loss products sold over the Internet found that all 9 had undeclared ingredients, 3 having sibutramine).

Kang JG, Park CY. Anti-Obesity Drugs: A Review about Their Effects and Safety. *Diabetes Metab J* 2012; 36: 13-25. PubMed PMID: 2363917.

(Review of the safety and efficacy of current and potentially future medications for obesity; mentions that the five year cardiovascular outcomes study of sibutramine [James 2010] demonstrated a significant increase in pulse, blood pressure, and risk of nonfatal myocardial infarction and stroke which led to its withdrawal in October 2010).