U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Beta-2 Adrenergic Agonists. [Updated 2017 Sep 11].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Beta-2 Adrenergic Agonists

Updated: September 11, 2017.

OVERVIEW

Introduction

The beta-2 adrenergic agonists are a large group of drugs that mimic the actions of naturally occurring catecholamines such as norepinephrine, epinephrine and dopamine. Direct agonists directly interact with the adrenergic receptors, whereas indirect agonists typically stimulate the release of endogenous catecholamines. The beta-2 adrenergic agonists act mainly on the smooth muscle of the vasculature, bronchial tree, intestines and uterus. These agents also act on the liver stimulating glycogenolysis and release of glucose from the liver and muscle (particularly if used in high doses). The beta-2 adrenergic agonists are used largely as bronchodilators in the management of asthma, both in control of acute symptomatic attacks as well as chronic, long term prevention and management. These agents are some of the most commonly prescribed drugs for asthma and are widely used and proven to be well tolerated and safe. The use of beta adrenergic agonists in asthma has not been associated with elevations in serum aminotransferase or alkaline phosphatase levels or in causing clinically apparent liver disease. When given in large doses or after intentional overdose, beta adrenergic agonists can cause liver injury. Most case reports of liver damage from these agents have been associated with their use in control of premature labor (for their effects on relaxation of uterine smooth muscle). The liver injury typically arises within a few days of starting high dose intravenous beta adrenergic agonists, is usually asymptomatic, not associated with jaundice, and rapidly reversed once the medication is stopped.

Commonly used beta adrenergic drugs include albuterol, bitolterol, metaproterenol, pirbuterol, salmeterol and terbutaline. These agents share structural similarity and are discussed together.

Beta Adrenergic Agonists Used for Asthma: Bitolterol, Formoterol, Metaproterenol, Pirbuterol, Salbutamol (Albuterol), Salmeterol, Terbutaline

The beta adrenergic agonists act on bronchial smooth muscle inducing bronchodilation and relieving bronchospasm in asthma and chronic obstructive pulmonary disease with asthmatic features. Their use in asthma has not been associated with liver injury.

Background

The beta adrenergic agonists are potent bronchodilators that are widely used in the management of bronchial asthma. These agents act by engaging the beta-2 adrenergic receptors on smooth muscle of bronchial tissue, relieving bronchospasm and reducing airway resistance. They also act on smooth muscle of the vascular system, intestines and uterus. Common forms of beta adrenergic agonists include albuterol, bitolterol, fenoterol, formoterol, levalbuterol, metaproterenol, salmeterol, pirbuterol and terbutaline, which all have similar

mechanisms of action, chemical structure, side effects and efficacy, but somewhat different pharmacokinetics allowing for differences in dosing regimens and duration of action. Most of these agents are administered by inhalation (alone or in combination with other bronchodilators or corticosteroids), with only albuterol and terbutaline being available in oral forms in the United States. Albuterol (also known as salbutamol) is available in generic forms and under the brand names of Proventil and Ventolin as 2 and 4 mg tablets as well as in aerosol and syrup solutions. The recommended regimen of albuterol is 2 to 4 mg orally 3 to 4 times a day. Sustained release formulations are available for twice daily dosing (4 and 8 mg). Salmeterol is available as an inhalation powder in generic forms and under the brand name of Serevent Diskus. The typical dosage is one inhalation (50 mcg) twice daily and it is recommended to be given with corticosteroids only. Systemic absorption is minimal. Terbutaline is available in generic forms and under the brand name of Brethine in tablets of 2.5 and 5 mg, the usual adult dosage being 5 mg three times daily. These oral forms of beta adrenergic agonists are approved as means of prevention and reversal of bronchospasm and are used largely in the therapy of asthma. Terbutaline is also available in parenteral formulations for use in acute bronchospasm and has also been used as therapy of premature labor. Common side effects of the beta adrenergic agonists include dizziness, headache, nervousness, tachycardia, palpitations, nausea and diaphoresis, largely due to their beta adrenergic effects on other organs. Rare, potentially severe adverse events include cardiovascular events, paradoxical worsening of asthma and acute hypersensitivity reactions.

Hepatotoxicity

Prospective studies have shown that ALT elevations occur in less than 1% of patients receiving long term oral therapy with typical beta adrenergic bronchodilators, but instances of clinically apparent liver injury have not been reported in any detail. However, several cases of acute elevations in serum aminotransferase levels have been described in pregnant women receiving high doses of beta adrenergic agents intravenously for prevention or control of premature labor (Case 1). Serum alkaline phosphatase, GGT and bilirubin levels are generally normal or within the normal range for later stages of pregnancy. The serum aminotransferase elevations are usually asymptomatic, but may be associated with nausea and right upper quadrant pain. Bilirubin elevations are minimal and cases with jaundice have not been reported. The abnormalities resolve promptly (within 1 to 3 weeks) upon stopping therapy and have not been associated with fatalities or chronic liver injury.

Likelihood score, oral beta-adrenergic agonists: E (unlikely cause of clinically apparent liver injury).

Likelihood score, intravenous terbutaline: C[H] (high doses of intravenous terbutaline are a probable cause of acute serum aminotransferase elevations that can be symptomatic and clinically apparent).

Mechanism of Hepatotoxicity

The mechanism of hepatic injury due to beta adrenergic agents is probably a direct hepatotoxicity associated with high dose, particularly intravenous, therapy.

Outcome and Management

Typically, liver enzyme abnormalities resolve rapidly after stopping beta adrenergic agents. No cases of fulminant hepatitis or chronic liver injury have been convincingly linked to use of these agents. The hepatotoxicity associated with high dose therapy is rapidly reversed and cases of recurrence upon reexposure to typical oral doses have not been reported.

Drug Class: Antiasthmatic Agents, Beta-2 Adrenergic Agonists

CASE REPORT

Case 1. Serum aminotransferase elevations during intravenous terbutaline therapy of premature labor.

[Modified from: Quinn PG, Sherman BW, Tavill AS, Gibas AL. Terbutaline hepatitis in pregnancy: report of two cases and literature review. Am J Gastroenterol 1994; 89: 781-4. PubMed Citation]

A 34 year old woman developed premature labor during her 26th week of pregnancy and was treated with intravenous terbutaline. Approximately 5 weeks later, she was admitted with generalized pruritus and found to have marked elevations in serum aminotransferase levels (ALT 223, AST 129), but normal alkaline phosphatase levels for pregnancy and no jaundice (bilirubin 0.4 mg/dL). An ultrasound showed a normal liver and biliary tree. Tests for hepatitis A, B and C were negative as were autoantibodies. The pruritus and liver test abnormalities were initially attributed to cholestasis of pregnancy, but rising ALT levels (Table) led to a tentative diagnosis of terbutaline induced hepatotoxicity. Terbutaline was stopped and serum aminotransferase levels promptly declined. However, uterine contractions increased and the patient delivered 3 healthy babies 3 days later. In follow up 3 weeks after delivery, serum aminotransferase levels were normal.

Key Points

Medication:	Terbutaline (intravenous, ~3 mg/day)
Pattern:	Hepatocellular (ALT elevations only)
Severity:	1+ (aminotransferase elevations without jaundice)
Latency:	5 weeks (elevated ALT)
Recovery:	<3 weeks
Other medications:	Ampicillin, cholestyramine, hydoxyzine, aspirin, docusate, ferrous sulfate, prednisone (10 mg/day)

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Terbutaline pump started at 26 weeks of gestation.					
39 days		223	267	0.4	
40 days		350			
41 days		620			
42 days		710			
44 days		2011	308	0.4	
45 days		1073			
47 days		950			Pruritus
50 days		1320			
51 days	0	920			Terbutaline stopped
53 days	2 days	710			
54 days	3 days	180			Caesarean delivery
10 weeks	3 weeks	20			
Normal Values		**<56**		**<1.2**	

* Values estimated from Figure 1, Patient 2.

Comment

The differential diagnosis of liver disease during pregnancy is challenging and includes viral hepatitis, cholestasis of pregnancy, acute fatty liver of pregnancy and drug induced liver disease. This patient was initially thought to have cholestasis of pregnancy with itching and abnormal serum enzyme elevations. However, the height of the ALT elevations with normal alkaline phosphatase levels and bilirubin were atypical of cholestasis of pregnancy and the role of terbutaline was considered. Acute fatty liver of pregnancy was excluded by the normal ultrasound. Stopping terbutaline led to a prompt decrease in ALT levels, but also triggered premature labor and delivery. The absence of bilirubin and alkaline phosphatase elevations supported the role of terbutaline induced liver injury in this patient. Asymptomatic but prominent elevations in serum aminotransferase levels have been reported with use of high doses of beta adrenergic agents in pregnant women.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Albuterol – Salbutamol, Proventil® HFA

Salmeterol – Serevent®

Terbutaline – Brethine®

DRUG CLASS

Antiasthmatic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

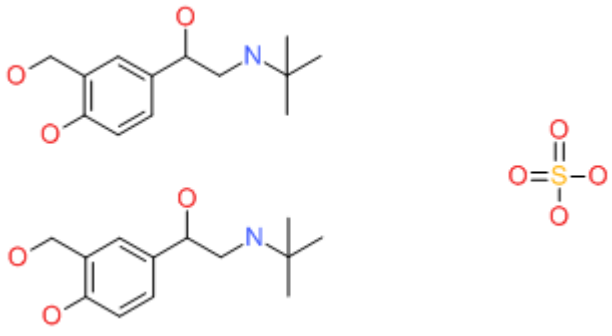
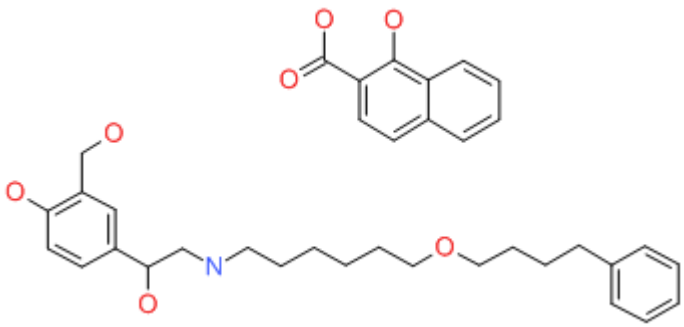
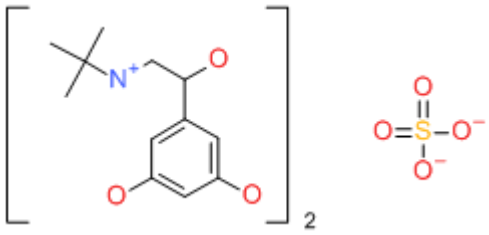
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Albuterol Sulfate	51022-70-9	C13-H21-N-O3.1/2H2-O4-S	

Table continued from previous page.

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Salmeterol Xinafoate	94749-08-3	C25-H37-N-O4.C11-H8-O3	
Terbutaline Sulfate	23031-32-5	C12-H19-N-O3.1/2H2-O4-S	

ANNOTATED BIBLIOGRAPHY

References updated: 11 September 2017

Zimmerman HJ. Adrenergic agents used as tocolytic (uterine relaxing) drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 715.

(Expert review of liver injury published in 1999, mentions that at least 3 cases of acute hepatocellular injury have been described after use of terbutaline to arrest premature labor).

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

(Textbook of pharmacology and therapeutics).

Suzuki M, Inagaki K, Kihira M, Matsuzawa K, Ishikawa K, Ishizuka T. Maternal liver impairment associated with prolonged high-dose administration of terbutaline for premature labor. Obstet Gynecol 1985; 66 (3 Suppl): 14S-15S. PubMed PMID: 4022509.

(32 year old pregnant woman with premature labor was treated with iv terbutaline and developed nausea and enzyme elevations [bilirubin 0.7 mg/dL, ALT 1000 U/L, Alk P 172 U/L] 1 week later, which fell to normal 2 weeks after stopping and 1 week after delivery).

Wilczyński J, Hauk-Szklarek E, Borowski P, Wysocki K, Kuydowicz J, Sałacińska B. [Increased activity of aminotransferases (ALAT, AspAT) in pregnant women threatened with immature and premature delivery treated with fenoterol] Ginekol Pol 1993; 64: 117-9. Polish. PubMed PMID: 835973.

Quinn PG, Sherman BW, Tavill AS, Gibas AL. Terbutaline hepatitis in pregnancy: report of two cases and literature review. Am J Gastroenterol 1994; 89: 781-4. PubMed PMID: 8172156.

(33 and 34 year old pregnant women developed marked ALT elevations [peaking at 910 and 2011 U/L] without jaundice after 4 weeks of terbutaline therapy [oral and iv], resolving within 3-4 days of stopping to near normal levels, whereupon delivery occurred: Case 1).

Fontaine P, Géhénot M, Goffin P, Horsmans Y. Fenoterol-induced hepatitis in a pregnant woman: a case report. Am J Obstet Gynecol 1996; 174: 1647-8. PubMed PMID: 9065147.

(27 year old woman developed acute elevations in ALT [peak 12 times ULN] with normal GGT and bilirubin levels during high dose fenoterol therapy for premature labor, resolving within 2 weeks of stopping fenoterol).

Edelman JM, Turpin JA, Bronsky EA, Grossman J, Kemp JP, Ghannam AF, DeLucca PT, at al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. A randomized, double-blind trial. Exercise Study Group. Ann Intern Med 2000;132: 97-104. PubMed PMID: 10644288.

(191 patients with exercise induced bronchospasm received either montelukast or salmeterol aerosol for 8 weeks; in discussion of safety there was no mention of liver side effects or ALT levels).

Ibanez I, Perez E, Vidal X, Laporte JR. Prospective surveillance of acute serious liver disease unrelated to infectious, obstructive, or metabolic diseases: epidemiological and clinical features, and exposure to drugs. J Hepatol 2002; 37: 592-600. PubMed Citation

(Prospective study of acute serious liver disease occurring over 6 years in Catalonia, Spain found 107 cases of drug induced liver injury, 3 of which were attributed to salbutamol [albuterol], but no clinical details given).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, no cases were attributed to albuterol or terbutaline or other oral or inhalational beta adrenergic agonists).