Journal of Toxicology: Clinical Toxicology

ISSN: 0731-3810 (Print) (Online) Journal homepage: http://www.tandfonline.com/loi/ictx19

Acute Beta Blocker Overdose: Factors Associated with the Development of Cardiovascular Morbidity

Jeffrey N. Love, Dr. Jeffrey Love, John M. Howell, Toby L. Litovitz & Wendy Klein-Schwartz

To cite this article: Jeffrey N. Love, Dr. Jeffrey Love, John M. Howell, Toby L. Litovitz & Wendy Klein-Schwartz (2000) Acute Beta Blocker Overdose: Factors Associated with the Development of Cardiovascular Morbidity, Journal of Toxicology: Clinical Toxicology, 38:3, 275-281, DOI: 10.1081/CLT-100100932

To link to this article: http://dx.doi.org/10.1081/CLT-100100932

Published online: 14 Jun 2000.

Clinical Toxicology, 38(3), 275–281 (2000)

ARTICLES

Acute Beta Blocker Overdose: Factors Associated with the Development of Cardiovascular Morbidity

Jeffrey N. Love; John M. Howell; Toby L. Litovitz; Wendy Klein-Schwartz

Georgetown University; Washington, DC (JNL, JMH); National Capital Poison Center, Washington, DC (TLL); Maryland Poison Center, University of Maryland, Baltimore, Maryland (WK-S)

ABSTRACT

Objective: To identify factors in exposures to beta blockers (beta-adrenergic receptor antagonists) that are associated with the development of cardiovascular morbidity and contribute to disposition decisions from the emergency department. Methods: Prospective cohort of 280 beta blocker exposures reported to 2 regional poison centers. Multiple logistic regression was used to determine association of various clinical factors and outcome. Results: In this series of beta blocker exposures, 41 (15%) developed cardiovascular morbidity and 4 (1.4%) died. A history of cardioactive coingestant was the only factor significantly associated with the development of cardiovascular morbidity ($p < .05$). When cases reporting cardioactive coingestants were excluded, a history of ingesting a beta blocker with membrane stabilizing activity was significantly associated with the development of cardiovascular morbidity ($p < .05$). All those in whom the timing of symptoms could be determined, developed symptoms within 6 hours of ingestion. Conclusions: The single most important factor associated with the development of cardiovascular morbidity in beta blocker ingestion is a history of a cardioactive coingestant, primarily calcium channel blockers, cyclic antidepressants, and neuroleptics. In the absence of such coingestion, exposure to a beta blocker with membrane stabilizing activity is as-

Correspondence: Dr. Jeffrey Love, Department of Emergency Medicine, Georgetown University Hospital, 3800 Reservoir Road, NW, Washington, DC 20007. Tel: 202/784-2050; Fax: 202/784-3019.

sociated with an increased risk of cardiovascular morbidity. Beta blocker ingestion is unlikely to result in symptoms if the patient remains asymptomatic for 6 hours after the time of ingestion.

INTRODUCTION

A recent review of American Association of Poison Center Toxic Exposure Surveillance System (TESS) data from 1985 to 1995 reported 52,156 exposures to beta blockers (beta-adrenergic receptor antagonists) over that time period.[1] An understanding of the risk factors that predispose to morbidity and mortality is important for proper evaluation, treatment, and disposition of beta blocker overdoses. Though respiratory depression, bronchospasm, and seizures may result from beta blocker intoxication, cardiovascular depression appears to be the most common cause of morbidity and mortality in the hospitalized patient.[1,2] The medical literature, based primarily on anecdotal experience, provides limited information regarding those at risk of cardiovascular morbidity. The identification of risk factors allows the emergency physician to identify patients at greatest risk while allowing early medical clearance for those who are not.

MATERIALS AND METHODS

Upon Institutional Review Board approval, data were collected prospectively beginning in January of 1992 at the first poison center and April of 1993 at the second, and continued through February of 1998. Patient data were collected by certified poison information specialists during the initial poison center consultation. A beta blocker questionnaire was initiated in each case to standardize and direct data collection. Statistical analysis was performed on the data collected using multiple logistic regression and forward stepwise technique, with SPSS, version 4.0 (SPSS, Inc, Chicago, IL). Alpha was set at 0.05. The dependent variable was cardiovascular morbidity and the following independent variables were assessed: age, gender, number of coingestants, membrane stabilizing potential of the beta blocker (MSA), acuity (acute on chronic vs single acute ingestion), therapeutic indication (for patients ingesting their own medications), common coingestants (ethanol, benzodiazepines, noncyclic antidepressants), and the presence of cardioactive coingestants.

Upon receiving the original request for consultation, one of the authors (JNL) was then contacted by the poison center and in most instances performed the next followup and coordinated subsequent progress reports. The goals were to complete data collection and ascertain the presence and timing of new symptoms consistent with beta blocker toxicity: bradycardia, hypotension, and therapy. Initially, followup occurred every 1–2 hours with the treating physician or nurse, and then less frequently, as the risk of toxicity development diminished, to no less then one progress report per day. Follow-up continued until the patient was discharged from the hospital or transferred to a psychiatric unit. When necessary, one of the authors (JNL) initiated discussions with treating physicians following selected clinical episodes to clarify details of complex cases.

This study targets calls to the poison center concerning potentially excessive beta blocker exposure in adults. Cases were considered for inclusion if:

1. There was a reported history of excessive exposure to beta blockers. Because it may be difficult to differentiate intentional from unintentional exposure upon clinical presentation, no attempt was made to do so in this study.

Exclusion criteria included:

1. Patients below the age of 6 years because exposures in this age group almost always involve a limited number of pills.

2. Patients assessed as having an adverse effect to their usual dose of beta blocker medication.

Cardiovascular morbidity was prospectively defined as:

1. Systolic blood pressure less than 90 mm Hg or heart rate less than 60 bpm, and

2. Symptoms suggesting decreased end-organ perfusion (e.g., diminished level of consciousness, chest pain), and

3. Therapeutic intervention involving cardioactive medications with recognized efficacy in beta blocker intoxication (e.g., atropine, glucagon, catecholamines). This did not include treatment with intravenous (IV) fluids alone.

Patients who did not meet all 3 of the above criteria were considered patients without cardiovascular morbidity. Quantitative assays (i.e., blood ethanol, digoxin, lithium) and qualitative drug screens (drugs of abuse) were used to verify the history if available to the physician in the emergency department. Verification of beta blocker ingestion and most cardioactive coingestants by serum

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

analysis was not used to impact the data because this information was not available to make disposition decisions. Cardioactive coingestants were defined as drugs that may cause cardiovascular depression similar to that noted with beta blockers (hypotension, bradycardia, heart block).

Cases were included for the timing of symptom onset if this information could clearly be established by history. Though excluded from grouped data, attention was also focused on any case where the timing of ingestion was uncertain but the history was clear that the patient was asymptomatic prior to presentation. If encountered, any instance of symptom development more than 6 hours after presentation would be reported as a possible episode of delayed onset of toxicity.

RESULTS

Over a period of approximately 5 to 6 years, the 2 participating regional poison centers provided consultation for 280 consecutive beta blocker exposures. Of these patients, 41 (15%) developed cardiovascular morbidity that required treatment with cardioactive medications and 4 (1.4%) died as a result of their exposure. Women comprised 62% (148/239) of patients without and 63% (26/41) of those with cardiovascular morbidity. No case of beta blocker exposure was reported in children from age 6 to 11 years of age over this time period.

There was a 100% collection rate in regard to age, gender, beta blocker ingested, and potential coingestants. A beta blocker had been prescribed for 193 subjects, while 61 patients ingested someone else's medication. The source was unclear in 26. Table 1 lists the therapeutic indications for the beta blocker prescription to patients who subsequently ingested their own medications.

Propranolol was the most common beta blocker implicated (121 of 280 exposures) and was most often responsible for cardiovascular toxicity (19/41). Propranolol, atenolol, and metoprolol were responsible for 87% (244/280) of beta blocker exposures (Table 2). Twenty-three exposures involved sustained-release preparations (20 propranolol, 3 metoprolol), 2 of which were symptomatic. A history of beta blockers with membrane stabilizing activity (MSA) was noted for 62% (174/280) of beta blocker exposures and 73% (30/41) of those demonstrating cardiovascular morbidity. In exposures without cardioactive coingestants, beta blockers with MSA were associated with 94% (15/16) of cases with cardiovascular toxicity (Table 2).

Beta blocker exposure was complicated by a history of at least 1 coingestant in 210 cases (73%). In 30% (83/280), 3 or more coingestants were reported and in 8% (22/280) 5 or more coingestants were noted. The most common coingestants were benzodiazepines, reported in

Table 1

Indications for Beta Blocker Therapy in Patients Ingesting Their Own Medication

Number of Cases	% of Known Indications	Therapeutic Indication
69	51.9	Cardiovascular disease (hypertension, arrhythmias, coronary artery disease, etc.)
23	17.3	Migraine headache prophylaxis
19	14.3	Relief of somatic complaints (anxiety, tremors, palpitations, etc.)
13	9.8	Psychotropic indications (akathisia induced by psychotropic medications, etc.)
6	4.5	Hyperthyroidism
3	2.3	Other (portal hypertension, glaucoma, etc.)
60		Indication unknown

Table 2

Number of Exposures and Cases That Developed Cardiovascular Morbidity in the Presence and Absence of Cardioactive Coingestants for Various Beta Blockers

	All Exposures		Exposures Without Cardioactive Coingestants	
Beta Blocker	**Number of Exposures**	**Cardiovascular Morbidity**	**Number of Exposures**	**Cardiovascular Morbidity**
*Propranolol	121 (43%)	19 (46%)	85 (44%)	8 (50%)
*Metoprolol	36 (13%)	7 (17%)	23 (12%)	4 (25%)
*Labetalol	12 (4%)	3 (7%)	10 (5%)	2 (13%)
*Acebutolol	4 (1%)	1 (2%)	3 (2%)	1 (6%)
*Pindolol	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Atenolol	87 (31%)	8 (20%)	61 (32%)	1 (6%)
Nadolol	8 (3%)	2 (5%)	4 (2%)	0 (0%)
Bisoprolol	5 (2%)	0 (0%)	3 (2%)	0 (0%)
Timolol	3 (1%)	0 (0%)	3 (2%)	0 (0%)
Sotalol	2 (<1%)	1 (2%)	0 (0%)	0 (0%)
Betaxolol	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Total	280	41	193	16

Percentages expressed represent the percentage of the total for that column. Drugs with membrane stabilizing action are marked with an asterisk (*). Cardioactive coingestants included: calcium channel blockers, cyclic antidepressants, neuroleptics, procainamide, angiotensin (ACE) inhibitors, digoxin, clonidine, and lithium.

20% (56/280) of exposures, and ethanol, reported in 19% (54/280). The reported cardioactive coingestants, listed in Table 3, were reported in 26% (62/239) of those without and in 61% (25/41) of those with cardiovascular morbidity.

Symptomatic bradycardia (heart rate less than 60 bpm) or hypotension (systolic blood pressure less than 90 mmHg) was noted in each case classified as having cardiovascular morbidity. In 24 patients, the time of onset could be determined; 22 developed cardiovascular toxicity within 3 hours and the remaining 2 patients were symptomatic on presentation between 3 and 6 hours postingestion. In 17 cases, the time to symptom onset was not clear. All 41 cases that developed cardiovascular morbidity did so prior to presentation or while in the emergency department. If asymptomatic at presentation, no patient developed symptoms consistant with beta blocker toxicity after more then 6 hours of observation in the emergency department.

The majority (75.4%; 211/280) of patients managed in the emergency department were admitted to a monitoring unit with medical clearance to a psychiatric unit or to a home for 20.7% (58/280). The remaining 3.1% of patients were either admitted to an unmonitored unit (6/280), left against medical advice (4/280), or died in the emergency department (1/280).

Among all cases, the only independent variable significantly associated with cardiovascular morbidity was a history of cardioactive coingestant ($p < .05$). Among patients without a cardioactive coingestant ($n = 193$), the history of ingestion of a MSA was significantly associated with cardiovascular morbidity while age, gender, acuity (acute on chronic versus acute single ingestion), therapeutic indication, number of coingestants, and a history of coingesting ethanol, benzodiazepines, and noncyclic antidepressants were not.

DISCUSSION

Beta blockers are used therapeutically for a wide range of indications. Potential toxicity from putative beta blocker ingestions is a common concern, 8553 exposures were reported to the American Association of Poison

Table 3

Frequency by History of Common Coingestants in Beta Blocker Exposures With (n = 41) and Without (n = 239) Cardiovascular Morbidity

Co-ingestant (by history)	Cases Without CV Morbidity # %	Cases With CV Morbidity # %
Benzodiazepines	49 21%	7 17%
Ethanol	46 19%	8 20%
Noncyclic antidepressants	29 12%	6 15%
Cardioactive medications	62 26%	25 61%
—Calcium channel blockers	(19)	(12)
—Cyclic antidepressants	(19)	(7)
—Neuroleptics	(17)	(9)
—ACE inhibitors	(13)	(2)
—Lithium	(9)	(2)
—Digoxin	(4)	(1)
—Clonidine	(3)	(1)
—Type Ia antiarrhythmics (Procainamide)	(0) —	(1) —

To be included as a cardioactive medication, there had to be at least one report associated with cardiovascular morbidity in this series. Those numbers in parenthesis are grouped together for the purpose of statistical analysis.

Control Centers TESS in 1997.[3] Estimates of the risk of morbidity and the need for hospitalization are often based on an unreliable history, yet these decisions are routinely made by the emergency physician and toxicologist. This study evaluates a continuous, prospective series of 280 beta blocker exposures reported over 5 years to 2 regional poison centers in an attempt to identify factors that predict the development of cardiovascular toxicity, the primary cause of morbidity, and mortality.

In this series of adults, 1 of every 6.7 reported beta blocker exposures developed cardiovascular morbidity requiring therapy with cardioactive medications. The single most important factor identified associated with cardiovascular morbidity was a history of a cardioactive coingestant. This finding is consistent with a recent review of beta blocker–related deaths that found calcium channel blockers and tricyclic antidepressants to be the most common coingestants in fatal beta blocker ingestions.[1] Whether the worsened outcomes observed with cardioactive coingestants result from a greater toxicity of these medications or an additive effect with beta blockers is unclear. Several studies suggest that calcium channel blockers, particularly verapamil, enhance the cardiovascular toxicity of beta blockers.[4-7] Both cyclic antidepressants and phenothiazines have MSA that has been hypothesized to enhance beta blocker toxicity.[8] Ethanol also possesses some MSA, raising similar concerns.[8,9] However, this study[9] did not find enhanced cardiovascular morbidity from the coingestion of beta blockers and ethanol. Similarly, benzodiazepines and a history of noncyclic antidepressant coingestion was not significantly associated with the development of cardiovascular morbidity.

Beta blocker toxicity is often ascribed to the presence of MSA, a property of propranolol, labetalol, acebutolol, metoprolol, and pindolol. When cases involving cardioactive coingestants were excluded, MSA was the only factor associated with cardiovascular toxicity. Indeed, 15 of 16 symptomatic beta blocker exposures without cardioactive coingestants involved agents with MSA. Atenolol was the second most commonly reported beta blocker exposure but was responsible for only 1 case of cardiovascular morbidity in the absence of such coingestants. Atenolol lacks MSA. No instances of cardiovascular morbidity developed in any of the other agents lacking MSA in the absence of a cardioactive coingestant. This prospective study corroborates the hypothesis concerning isolated beta blocker expo-

sures: although hemodynamic compromise can result from beta blockers without MSA, such instances appear to be much less common than with MSA.[1,7]

Cardiovascular toxicity developed in 15% of all beta blocker exposures. All those who developed symptoms did so in the emergency department or prior to presentation. No patient developed symptoms after hospitalization; yet, 75.4% of exposures were admitted to a monitored unit. The decision to admit to a critical care unit is multifactorial and difficult to assess. Although several hospital admissions were based on toxicity unrelated to the beta blocker, the majority appeared to result from concern about delayed hemodynamic instability. No patient without cardiovascular morbidity was admitted for other sequelae of beta blocker toxicity such as seizures or bronchospasm.

Toxicity from beta blocker exposure generally develops within 2 hours of ingestion.[10] A review of the literature[11] and a subsequent report[12] suggest that patients who develop signs and symptoms of toxicity do so within 6 hours of ingestion. Our study substantiates these findings. Patients with probable beta blocker overdoses who remain asymptomatic and demonstrate no sign of hemodynamic instability for 6 hours after ingestion appear to be at little risk of subsequent deterioration.

Several important exceptions to medical clearance at 6 hours postingestion may exist. The patient's history plays an important role in determining the need for hospitalization in these instances. Cardioactive coingestants not only increase the risk of hemodynamic instability, they further complicate disposition decisions in several ways. Asymptomatic ingestion of sustained-release verapamil[13] and some angiotensin-converting enzyme (ACE) inhibitors[14] may require observation for a period of longer than 6 hours. The interaction of large doses of beta blockers with other cardioactive medications has not been well studied, and it is not known whether such an interaction impacts the timing of symptoms. For these reasons, a beta blocker exposure with cardioactive coingestant is more likely to warrant hospital admission and monitored observation. Another concern is sustained-release beta blocker preparations. The current study includes 23 such exposures of which 2 were symptomatic. Although there are no reports in the literature of delayed symptom onset with sustained-release products, the risk of symptom development beyond a 6-hour period is unclear. Finally, although not defined in the limited number of exposures of our study, sotalol has a unique Type III antiarrhythmic activity and long half-life that pose patients at significant risk of delayed toxicity.[15] The need for observation beyond 6 hours in the asymptomatic sotalol ingestion should be based on the QTc interval.[15]

This study involves the capture and analysis of patient data gathered at the time of poison center consultation. As such, these data have inherent limitations common to Poison Control Center (PCC) studies including possible selection bias and potential incomplete reporting of information. It is generally believed that more severe cases are reported to poison centers. If this is true, our data may overestimate the likelihood of symptoms following exposure. The second common limitation of PCC data, incomplete reporting of data, is potentially consequential although minimized by the prospective design. Caution should be exercised when attempting to generalize these findings to children since the youngest participant in this series was 12 years of age.

Finally, this study was designed to determine which patients with a history of beta blocker exposure are at the greatest risk of cardiovascular morbidity. Only the variables normally available to the emergency physician were evaluated. Quantitative drug assays were not available to corroborate the history. Despite these limitations, we believe the observations are relevant to the common scenario of the asymptomatic patient with a history of beta blocker ingestion.

ACKNOWLEDGEMENT

Special thanks to the specialists of The National Capital and Maryland Poison Centers without whose support this study would not have been possible.

REFERENCES

1. Love JN, Litovitz TL, Howell JM, *et al*. Characterization of fatal beta blocker ingestion: A review of the American Association of Poison Control Centers Data from 1985–1995. *J Toxicol Clin Toxicol* 1997;**35**:353–359.
2. Weinstein RS. Recognition and management of poisoning with beta-adrenergic blocking agents. *Ann Emerg Med* 1984;**13**:1123–1131.
3. Litovitz TL, Klein-Schwartz W, Dyer KS, *et al*. 1997 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 1998;**16**:443–497.
4. Vick JA, Kandil A, Herman EH, *et al*. Reversal of propranolol and verapamil toxicity by calcium. *Vet Hum Toxicol* 1983;**25**:8–10.
5. Hamann SR, Kaltenborn KE, Vore M, *et al*. Cardiovascular and pharmacokinetic consequences of combined ad-

ministration of verapamil and propranolol in dogs. *Am J Cardiol* 1985;**56**:147–156.
6. Carruthers SG, Freeman DJ, Bailey DG. Synergistic adverse hemodynamic interaction between oral verapamil and propranolol. *Clin Pharmacol Ther* 1989;**46**:469–477.
7. Packer M, Meller J, Medina N, *et al*. Hemodynamic consequences of combined beta-adrenergic and slow calcium channel blockade in man. *Circulation* 1982;**65**: 660–668.
8. Henry JA, Cassidy SL. Membrane stabilizing activity: A major cause of fatal poisoning. *Lancet* 1986;1414–1417.
9. Nicolas F, Villers D, Rozo L, *et al*. Severe self-poisoning with acebutolol in association with alcohol. *Critical Care Med* 1987;**15**:173–174.
10. Frishman W, Jacob H, Eisenberg E, *et al*. Clinical pharmacology of the new beta-adrenergic blocker drugs. Part 8. Self-poisoning with beta-adrenoreceptor blocking agents: Recognition and management. *Am Heart J* 1979; **98**:798–811.
11. Love JN. Beta blocker toxicity after overdose: When do symptoms develop in adults? *J Emerg Med* 1994;**12**:799–802.
12. Reith DM, Dawson AH, Whyte IM, *et al*. Relative toxicity of beta blockers in overdose. *J Toxicol Clin Toxicol* 1996;**34**:273–278.
13. Ramoska EA, Spiller HA, Winter M, Borys D. A one year evaluation of calcium channel blocker overdoses: Toxicity and treatment. *Ann Emerg Med* 1993;**22**:196–200.
14. Augenstein WL, Kulig KW, Rumack BH. Captopril overdose resulting in hypotension. *JAMA* 1988;**259**:3302–3305.
15. Neuvonen PJ, Elonen E, Vuorenmaa T, *et al*. Prolonged QT interval and severe tachyarrhythmias, common features of sotalol intoxication. *Eur J Clin Pharmacol* 1981; **20**:85–89.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016