5. Larsen S, Zaric D, Boysen G: Postoperative cerebrovascular accidents in general surgery. Acta Anaesthesiol Scand 32:698–701, 1988

6. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. 4th edition. Washington, DC, American Psychiatric Association, 1994, pp 471–475

7. Pope HG, Jonas JM, Jones B: Factitious psychosis: Phenomenology, family history, and long-term outcome of nine patients. Am J Psychiatry 139:1480–1483, 1982

8. Arnold SE, Kumar A: Reversible dementias. Med Clin North Am 77:215–230, 1993

9. Ford CV, King BH, Hollender MH: Lies and liars: Psychiatric aspects of prevarication. Am J Psychiatry 145:554–562, 1988

10. Eisendrath SJ: Factitious physical disorders. West J Med 160: 177–179, 1994

11. Teasell RW, Shapiro AP: Strategic-behavioral intervention in the treatment of chronic nonorganic motor disorders. Am J Phys Med Rehabil 73:44–50, 1994

12. Reich P, Gottfried L: Factitious disorders in a teaching hospital. Ann Intern Med 99:240–247, 1983

13. Aduan RP, Fauci AS, Dale DC, Herzberg JH, Wolff SM: Factitious fever and self-induced infection: A report of 32 cases and review of the literature. Ann Intern Med 90:230–242, 1979

Anesthesiology
83:204–207, 1995

Successful Pharmacologic Treatment of Massive Atenolol Overdose: Sequential Hemodynamics and Plasma Atenolol Concentrations

Luiz G. R. DeLima, M.D., Evan D. Kharasch, M.D., Ph.D.,† Stephen Butler, M.D.‡*

ATENOLOL is a non-lipid-soluble β-adrenergic blocker, with greater selectivity for β1-adrenergic receptors.[1] It lacks intrinsic sympathomimetic activity or properties.[1] Only eight cases of atenolol poisoning have been reported in the English-language literature,[2–9] and in a recent report, hemodialysis was advocated to treat atenolol overdose.[2] We report a case of massive atenolol overdose and successful treatment by aggressive pharmacologic intervention only, and present sequential plasma atenolol concentrations and hemodynamic data. Our results show a marked improvement resulting from the administration of glucagon and call into question the need for instituting hemodialysis instead of aggressive pharmacologic management of such patients.

* Assistant Professor of Anesthesiology, University of Mississippi Medical Center.

† Associate Professor of Anesthesiology; Adjunct Associate Professor of Medicinal Chemistry, University of Washington.

‡ Associate Professor of Anesthesiology, University of Washington.

Received from the Department of Anesthesiology, University of Washington, Seattle, Washington, and the Department of Anesthesiology, University of Mississippi Medical Center, Jackson, Mississippi. Submitted for publication December 6, 1993. Accepted for publication March 9, 1995.

Address reprint requests to Dr. DeLima: Department of Anesthesiology, University of Mississippi Medical Center, 2500 North State Street, Jackson, Mississippi 39216-4505.

Key words: Blood: hemodynamics. Heart: coronary stenosis. Hormones: glucagon. Measurement techniques: gas chromatography-mass spectrometry. Sympathetic nervous system: atenolol; β-adrenergic receptors.

Case Report

A 50-yr-old, 98-kg man with a history of depression, coronary artery disease, hypertension, and asthma was brought to the our institution's emergency department after having allegedly ingested 20 atenolol tablets (50 mg/tablet) 30 min earlier. On arrival, he was alert and cooperative. Blood pressure was 130/80 mmHg, heart rate was 72 beats/min, respiratory rate was 24 breaths/min, and tympanic temperature was 36.6°C. Physical examination was otherwise unremarkable. An electrocardiogram showed sinus rhythm with a ventricular rate of 72 beats/min. A chest roentgenogram was normal. Laboratory data revealed sodium 141 mmol/L, potassium 4.9 mmol/L, chloride 104 mmol/L, HCO_3 18 mmol/L, blood urea nitrogen 12 mg/dL (4.28 mmol/l), creatinine 1.2 mg/dL (106 μmol/L), glucose 116 mg/dL (6.44 mmol/l), and hemoglobin 160 g/l. Routine toxicologic screening was negative. Gastric lavage was instituted without recovery of tablet fragments. An external pacemaker was applied. Electrocardiogram and oscillometric blood pressure monitoring were instituted, and for the next 90 min, a sinus rhythm at a rate of 60 beats/min and blood pressure between 110/70 mmHg and 120/80 mmHg were observed. Two hours after admission, the patient collapsed while having a bowel movement. Despite a total of 2 mg atropine, 1 mg glucagon, and 1,900 ml crystalloid, systolic blood pressure remained less than 80 mmHg. The electrocardiogram showed

sinus rhythm at a rate between 40 and
consciousness varied from unresponsiv
piratory wheezes were heard, and the
Three hours after admission, his trache
transferred to the intensive care unit
dose of 2 mg atropine, 1 mg glucagon,
1.5 μg/min norepinephrine. Arterial blo
taken immediately after intubation (m
self insufflating bag, 6 l/min O_2 enri
Pa_{CO_2} 74 mmHg, Pa_{O_2} 206 mmHg, and
was inserted into the radial artery, an
started. Arterial blood gas analysis w
respiratory rate of 16 breaths/min, ti
1.0, revealed *p*H 7.23, P_{CO_2} 33 mmHg
14 mmol/l. A balloon-tipped pulmona
Pharmacologic management consisted
cagon infusion, and isoproterenol in
given *via* a metered dosed inhaler
intensive care unit transfer (6 h after h

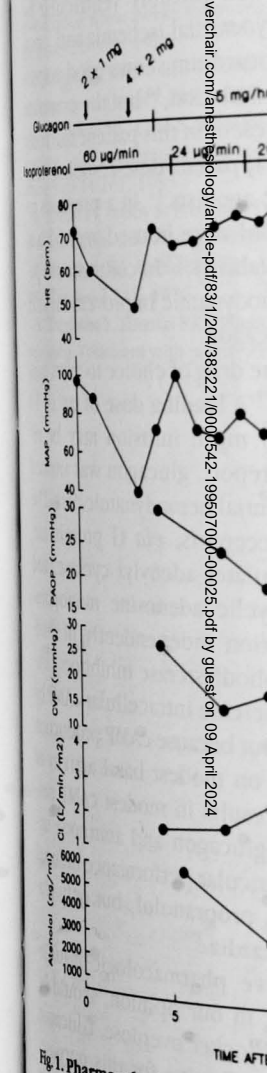

Fig. 1. Pharmacologic manageme
and plasma atenolol concentra

sinus rhythm at a rate between 40 and 50 beats/min. The level of consciousness varied from unresponsiveness to combativeness. Expiratory wheezes were heard, and the skin was cold and mottled. Three hours after admission, his trachea was intubated and he was transferred to the intensive care unit after receiving an additional dose of 2 mg atropine, 1 mg glucagon, 60 μg/min isoproterenol, and 13 μg/min norepinephrine. Arterial blood gas analysis from a sample taken immediately after intubation (manual ventilation with Ambu self insufflating bag, 6 l/min O_2 enrichment) revealed *p*H 6.85, Pa_{CO_2} 74 mmHg, Pa_{O_2} 206 mmHg, and HCO_3 13 mmol/l). A catheter was inserted into the radial artery, and mechanical ventilation was started. Arterial blood gas analysis with the lungs ventilated at a respiratory rate of 16 breaths/min, tidal volume 900 ml, and $F_{I_{O_2}}$ 1.0, revealed *p*H 7.23, P_{CO_2} 33 mmHg, Pa_{CO_2} 136 mmHg, and HCO_3 14 mmol/l. A balloon-tipped pulmonary artery catheter was inserted. Pharmacologic management consisted of glucagon bolus doses, glucagon infusion, and isoproterenol infusion (fig. 1). Albuterol was given *via* a metered dosed inhaler and spacer. Three hours after intensive care unit transfer (6 h after hospital admission), the patient regained consciousness and expiratory wheezes were no longer present. The trachea was extubated the following morning. Recovery proceeded uneventfully, all drugs were discontinued over the next 12 h, and he was discharged to a psychiatric ward. Blood creatinine concentration remained between 0.9 and 1.7 mg/dl (79.5 and 150.2 μmol/l, respectively) throughout the hospitalization. Creatinine clearance during the first 24 h was 68 ml/min. Atenolol plasma concentrations and hemodynamic profiles are summarized in figure 1.

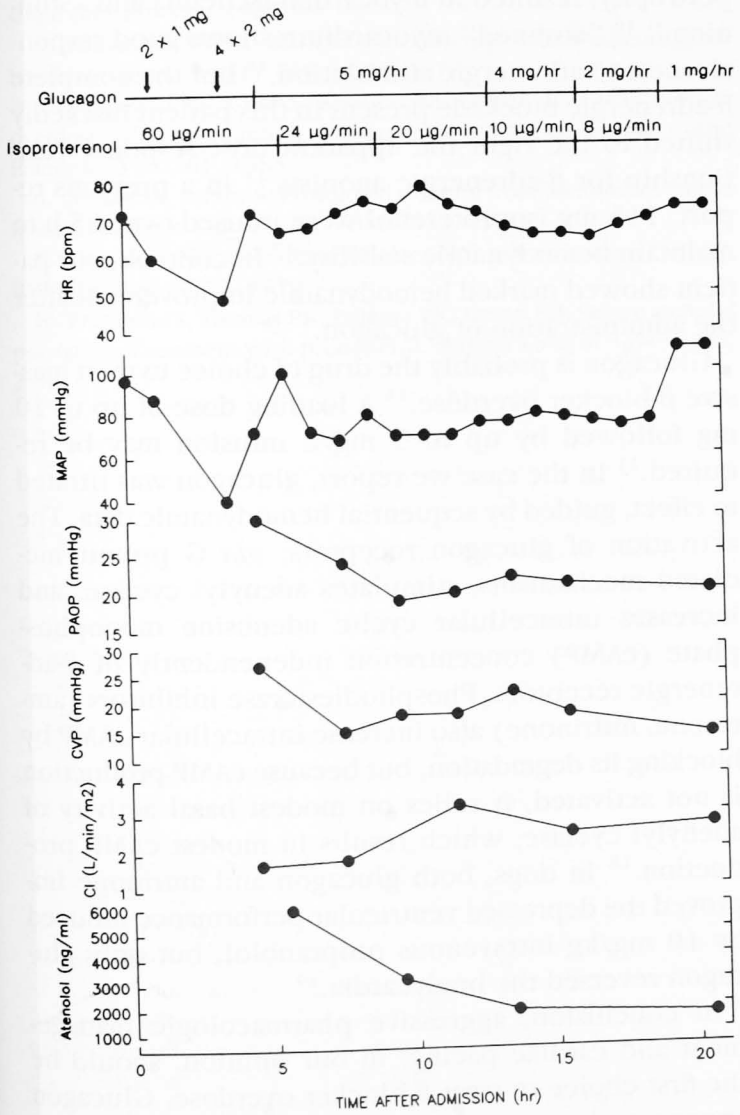

Fig. 1. Pharmacologic management, hemodynamic parameters, and plasma atenolol concentrations.

Atenolol Assay

Plasma atenolol concentrations were determined by gas chromatography-mass spectrometry with selected-ion monitoring, by modification of a previously described assay[10] and using metoprolol as an internal standard. Briefly, plasma (100 μl) was added to a PTFE-lined screw-cap tube containing 900 of μl water, 25 ng metoprolol, and 0.36 g sodium chloride, followed by 100 μl 1 M NaOH, 50 μL 2 M phosphate buffer (*p*H 11.5), and 10 ml methylene chloride. The mixture was vortexed for 30 s, shaken for 10 min, and centrifuged. The organic layer was evaporated to dryness under nitrogen, the residue dissolved in 100 μl ethyl acetate, and 25 μl pentafluoropropionic anhydride added. The reaction mixture was kept at 60°C for 30 min, evaporated to dryness under nitrogen, and reconstituted in 100 μl ethyl acetate, and 1–2 μl was injected into the gas chromatograph.

A Hewlett-Packard 5971A gas chromatograph-MSD equipped with a split-splitless injector was used with a 15 m × 0.32 mm × 0.25-μ DB-5 capillary column (J & W Scientific, Folsom, CA). The carrier gas was helium at 60 ml/min flow rate. Injector (splitless) and transfer line temperatures were 250°C and 260°C, respectively. The oven temperature was held at 50°C for 0.5 min, then increased to 250°C at 20°C per min. The dipentafluoropropionyl derivatives of metoprolol and atenolol were monitored at the base peak for each compound (ion at mass-to-charge ratio of 366). Atenolol was quantitated using a standard curve of the atenolol/metoprolol peak area ratio *versus* atenolol added (200–5,000 ng/ml), constructed with blank plasma spiked with known concentrations of atenolol. The standard curve was linear over this concentration range ($r^2 = 0.996$).

Discussion

Considering that the oral bioavailability of atenolol is approximately 40% of the ingested dose, peak plasma concentrations occur 1–2 h after oral administration,

and the elimination half-life is 6–9 h[1] and extrapolating the measured plasma concentrations to the time of peak effect one would predict this patient had a peak atenolol plasma concentration of 10,000 ng/ml which also coincides with the predicted peak concentration after ingesting 1,000 mg of the drug. Therapeutic plasma concentrations of atenolol are 200–500 ng/ml.[1]

The usual clinical manifestations of β-adrenergic blocker overdose include bradycardia, hypotension, low cardiac output, cardiac failure, and cardiogenic shock.[11] Bronchospasm[11] and respiratory depression[3,11] also may occur. Seizures and prolonged intraventricular conduction are thought to be the result of the local anesthetic properties of intoxication with certain β-adrenergic blockers (propranolol, acebutolol, alprenolol, oxprenolol) but not atenolol.[1,11] Hypoglycemia is reported to be rare.[11]

Patients vary in their responses to β-adrenergic blockers. As much as 4,000 mg/day of propranolol have been well tolerated,[4] whereas 40 mg of the same drug precipitated pulmonary edema in patients with occult cardiomyopathy.[11] In a previous report, an atenolol overdose of 5,000 mg resulting in a plasma concentration of 9,400 ng/ml, produced marked ventilatory depression requiring mechanical ventilation but only a sinus bradycardia to 59 beats/min, and hemodynamic stability was maintained without medication.[3] Hemodynamic instability, responsive to intravenous sympathomimetic or parasympatholytic support, was present in three cases of atenolol overdose, and another patient was treated with hemodialysis and pharmacologic support.[2] That case, complicated by hemodynamic instability and oliguria/anuria, apparently was unresponsive to pharmacologic support and cardiac pacing.[2] However, the hemodynamic data included only heart rate and blood pressure, the regime of isoproterenol and glucagon administration was unclear, and a single atenolol plasma concentration was reported (2,500 ng/ml), making it difficult to establish true unresponsiveness to conventional pharmacologic treatment. Additionally, hemodialysis requires large-bore vascular access and specialized personnel and may be complicated by hypotension, which is common in critically ill patients.[12,13]

Hemodynamic depression induced by β-adrenergic blocker overdose usually is responsive to sympathomimetics, parasympatholytics, glucagon, phosphodiesterase inhibitors, and cardiac pacing.[11] However, our patient did not show hemodynamic improvement with 60 μg/min isoproterenol and 13 μg/min norepinephrine. Norepinephrine was chosen for its α-adrenergic effect to increase blood pressure and possibly improve myocardial perfusion.[11]

In addition to myocardial depression, the hypotension observed with β-adrenergic blocker overdose is due in part to blockade of presynaptic β_2-adrenergic receptors that, when activated, increase neurotransmitter release in sympathetic nerve endings.[14] During massive atenolol overdose β_2-adrenergic blockade is likely to occur because the ratio of β_1 to β_2 selectivity of atenolol is 5.5.[15] It is also reasonable to speculate that, in the presence of decreased myocardial contractility caused by β-adrenergic blockade, the vagal stimulation or decreased venous return as a result of increased intra-abdominal pressure associated with defecation precipitated cardiovascular collapse, which, in the setting of coronary artery disease and possibly ventricular hypertrophy, resulted in myocardial ischemia and "stunning."[16] "Stunned" myocardium shows good responsiveness to adrenergic stimulation,[16] but the complete β-adrenergic blockade present in this patient markedly shifted to the right the apparent dose-response relationship for β-adrenergic agonists.[11] In a previous report, 115 mg isoproterenol were infused over 65 h to maintain hemodynamic stability.[17] In contrast, our patient showed marked hemodynamic improvement after the administration of glucagon.

Glucagon is probably the drug of choice to treat massive β-blocker overdose.[11] A loading dose of up to 10 mg followed by up to 5 mg/h infusion may be required.[11] In the case we report, glucagon was titrated to effect, guided by sequential hemodynamic data. The activation of glucagon receptors, *via* G protein-mediated mechanisms, stimulates adenylyl cyclase, and increases intracellular cyclic adenosine monophosphate (cAMP) concentration independently of β-adrenergic receptors. Phosphodiesterase inhibitors (amrinone, milrinone) also increase intracellular cAMP by blocking its degradation, but because cAMP production is not activated, it relies on modest basal activity of adenylyl cyclase, which results in modest cAMP production.[18] In dogs, both glucagon and amrinone improved the depressed ventricular performance induced by 10 mg/kg intravenous propranolol, but only glucagon reversed the bradycardia.[19]

In conclusion, aggressive pharmacologic management and cardiac pacing, in our opinion, should be the first choice to treat β-blocker overdose. Glucagon appears to be particularly effective for this purpose. Hemodialysis should be reserved to remove minimally

protein-bound, renally excreted β-blockers in cases refractory to pharmacologic therapy. It remains to be seen if earlier detection and treatment of cardiorespiratory depression can prevent cardiovascular collapse in these patients.

References

1. Frishman WH: Pharmacodynamic and pharmacokinetic properties, Clinical Pharmacology of the β-Adrenoceptor Blocking Drugs. Edited by Frishman WH. New York, Appleton-Century-Crofts, 1980, pp 1–14

2. Saitz R, Williams BW, Farber HW: Atenolol-induced cardiovascular collapse treated with hemodialysis. Crit Care Med 19:116–118, 1991

3. Montgomery BA, Stager MA, Schoene RB: Marked suppression of ventilation while awake following massive ingestion of atenolol. Chest 88:920–921, 1985

4. Boakes AJ, Boerre BH: Suicidal attempts with β-adrenoceptor blocking agents (letter). BMJ 4:675, 1973

5. Weinstein RS, Cole S, Knaster HB, Dahlbert T: Beta blocker overdose with propranolol and atenolol (two case reports). Ann Emerg Med 14:161, 1985

6. Abbasi IA, Sorsby S: Prolonged toxicity from atenolol overdose in an adolescent. Clin Pharm 5:836–837, 1986

7. Shanahan FLJ, Counihan TB: Atenolol self-poisoning (letter). BMJ [Clin Res] 2:773, 1978

8. Freestone S, Thomas RK, Bhamra RK, Dyson EH: Severe atenolol poisoning: Treatment with prenalterol. Human Toxicol 5:343–345, 1986

9. Giang D, Isaeff DM: Atenolol overdose in a patient with progressive renal failure. West J Med 145:101–103, 1986

10. Ervik M, Kylbert-Hanssen K, Lagerstrom PO: Electron-capture-gas chromatographic determination of atenolol in plasma and urine, using a simplified procedure with improved selectivity. J Chromatogr 182:341–347, 1980

11. Frishman WH, Jacob H, Eisenberg E, Ribner H: Clinical pharmacology of the new β-adrenergic blocking drugs: Self-poisoning with β-adrenoceptor blocking agents: Recognition and management. Am Heart J 98:798–811, 1979

12. Henderson LW: Symptomatic hypotension during hemodialysis (editorial review). Kidney Int 17:571–576, 1980

13. Huyghebaert M-F, Dhainaut J-F, Monsallier JF, Schlemmer B: Bicarbonate hemodialysis of patients with acute renal failure and severe sepsis. Crit Care Med 13:840–843, 1985

14. Boudreau G, Peronnet F, De Champlain J, Nadeau R: Presynaptic effects of epinephrine on norepinephrine release from cardiac sympathetic nerves in dogs. Am J Physiol 265(Heart Circ Physiol 34):H205–H211, 1993

15. Bilski AJ, Halliday SE, Fitzgerald JD, Wale JL: The pharmacology of a B_2-selective adrenoceptor antagonist (ICI 118, 551). J Cardiovasc Pharmacol 5:430–437, 1983

16. Bolli, R: Myocardial "stunning" in man. Circulation 86:1671–1691, 1992

17. Lagerfelt J, Matell G: Attempted suicide with 5.1G of propranolol: A case report. Acta Med Scand 199:517, 1976

18. Bristow MR, Hershberger RE, Port JD, Gilbert EM, Sandoval A, Rasmussen R, Cates AE, Feldman AM: Beta-adrenergic pathways in nonfailing and failing human ventricular myocardium. Circulation 82:I12–I25, 1990

19. Love JN, Leasure JA, Mundt DT, Janz TG: A comparison of amrinone and glucagon therapy for cardiovascular depression associated with propranolol toxicity in a canine model. J Toxicol Clin Toxicol 30:399–412, 1992