ATENOLOL/ PROPRANOLOL

Since their initial development for the treatment of angina pectoris and cardiac dysrhythmias in the 1960s, the therapeutic indications for beta adrenergic receptor antagonists have tremendously increased. The wide variety of clinical indications for beta blockers has made them ubiquitous in the treatment of patients. As the use of these agents increases, the incidence of beta blocker toxicity also increases. There were approximately 5300 ingestions reported to the AAPCC surveillance TESS data set in 1992 and about 8700 ingestions reported in 1998. Even though patients with beta blocker exposures can remain asymptomatic and have an uneventful clinical course, a review of AAPCC data between 1985 and 1995 showed that these drugs were involved in 2.5% of all poisoning-related fatalities. Propranolol has the distinction of being the drug within the class that is implicated most commonly in beta blocker overdose and the one most associated with severe morbidity and mortality. Propranolol, related structurally to isoproterenol, was also the first beta blocker synthesized. Atenolol, another member of the class, was developed to address the limitations found through clinical experience with propranolol. Compared to propranolol, atenolol has a much lower rate of fatalities. This Clinical Toxicology Review will compare these two different beta blockers.

Clinical Pharmacology

The major therapeutic action of beta-adrenergic blocking agents is their competitive displacement of endogenous and exogenous agonists from beta receptors on the myocardium, thereby reducing the activation of membrane adenylate cyclase. The resulting decrease in intracellular cyclic AMP exerts depressive effects on the myocardium. However, in the absence of severe primary heart disease, the fatalities associated with beta blocker toxicity cannot be readily explained by the total blockade of beta adrenergic receptors. Properties other than beta blockade, known or unknown, may play important roles in the toxicity of these drugs.

Beta blockers can be categorized according to their cardioselectivity, membrane stabilizing activity (MSA), partial agonist effects, and lipid solubility. Atenolol is a hydrophilic, selective beta blocker without any partial agonist or membrane stabilizing activity while propranolol is a lipophilic, non-selective beta-blocker possessing MSA and none of the partial agonist effect. A review of literature conducted by Critchley et al. stated that in beta blocker overdose, membrane stabilizing action is important, cardioselectivity tends to be lost and any partial agonist activity may be protective. In overdose, the membrane stabilizing effect results in reducing the cardiac membrane permeability for the fast inward current of sodium ions, thus preventing the triggering of cardiac muscle contraction.

Atenolol's half-life is six to nine hours, its apparent volume of distribution is 0.7 L/kg of body weight, and its binding to plasma protein is only 3% to 15%. Propranolol's half-life averages three to six hours, its apparent volume of distribution is 3.9 L/kg, and it is 93% bound to plasma protein. Compared to atenolol, propranolol's high morbidty and mortality are attributed to its MSA and lipophilicity. It has much greater penetration into the central nervous system because of its fat solubility.

In addition to a beta blocker’s pharmacologic activities, concurrent liver and renal impairment may influence its pharmacokinetics and thereby its toxicity. Atenolol is renally eliminated unchanged in the urine; intoxication may thus occur in patients with renal impairment. By contrast, propranolol is metabolized to an inactive metabolite by the liver and undergoes significant first pass metabolism. Patients in liver failure or with chronic cirrhosis may be at higher risk for toxicity due to their inability to detoxify the parent compound in a normal fashion.

Symptoms In Overdose

The absorption of both atenolol and propranolol after ingestion is rapid. While the onset of symptoms can occur in 20 to 60 minutes, symptoms of toxicity usually appear within 2 to 6 hours of ingestion.

As an extension of their pharmacologic activity, cardiac depression is the most common manifestation of beta blocker overdose. Common clinical features of toxicity shared by atenolol and propranolol are hypotension and bradycardia. However, with atenolol toxicity, the heart rate can remain within normal limits even in the presence of hypotension. On EKG conduction delays are often manifested as a prolonged PR interval (first degree block).

The less frequently occurring manifestations shared by both drugs are respiratory depression, hypoglycemia, bronchospasm and depressed level of consciousness that range from drowsiness to coma. The occurrence of an acute psychotic episode has also been reported to be the result of propranolol overdose.

The likelihood of bronchoconstriction and hypoglycemia depends on the underlying disease. As stated previously cardiovascularity is lost when the drugs are ingested in overdose. The hypoglycemic effect and the bronchospasm are mediated primarily by the B2 receptor. Hypotension is mostly due to the negative inotropic effect of the heart. In propranolol overdose, the membrane stabilizing effect may produce systemic vasodilatation and reduced peripheral vascular resistance, thus aggravating any hypotension resulting from the cardiodepressive effect. The decreased level of consciousness is usually attributed to decreased cerebral perfusion which results from hypotension, or alternately, to a direct effect on the central nervous system. Respiratory depression is most probably a consequence of a centrally-mediated depressive ventilatory response to CO.

Propranolol can result in severe conduction disturbances, seizures, and progressive heart block, which are not seen with atenolol poisoning. The seizure, usually generalized and brief, is due to the combination of hypoxia and membrane stabilizing effects of propranolol. In propranolol poisoning, seizures are a dose dependent phenomenon. The risk of seizure is higher in patients ingesting a minimum of 1.5 grams of propranolol and those with a QRS >100 ms. Conduction abnormalities are mostly manifested on the EKG as prolongation of the QRS complex. Sometimes, ST segment elevation, early repolarization, and peaked T waves may be the only EKG manifestations of propranolol's cardiotoxicity.

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Laboratory Assessment

The dose of a beta blocker ingested may not always correlate with the severity of symptoms seen in toxicity. Propranolol and atenolol blood levels can be determined using high-pressure liquid chromatography (HPLC) or gas chromatography/mass spectrometry (GC/MS). These assays are not generally available through commercial laboratories in a timely fashion. Blood levels do not appear to correlate well with therapeutic or toxic activity; thus tissue assays do not aid in clinical management. Though blood levels could be used to identify the offending agent in a symptomatic ingestion of unknown etiology, the diagnosis of beta blocker intoxication should be made on clinical grounds.

Treatment

As with any toxicity, the first priority in the treatment of poisoning due to propranolol or atenolol is evaluation of the “ABCs” (airway, breathing, and circulation) and supportive care. In patients with seizures resulting from propranolol ingestion, administration of an anti-convulsant such as a benzodiazepine should be considered. In an attempt to minimize GI absorption, activated charcoal should be administered to all patients. Multiple dose activated charcoal (gut dialysis) is probably more beneficial in atenolol than propranolol intoxication since propranolol has a high protein binding capacity. Ipecac is contraindicated due to the risk of altered mental status and seizures associated with beta blocker ingestion. Aside from being implicated in starting seizures, ipecac-induced vomiting increases the risk of aspiration and the vagal effect can worsen conduction disturbances. Gastric lavage, with atropine as premedication, could be performed if the patient presents within 30 minutes of ingestion. The risk of excessive vagal stimulation argues for caution when the clinician is weighing the benefit of gastric lavage. Hemodialysis may be useful in a renal impaired patient intoxicated with atenolol, but is not useful in propranolol overdose.

Pharmacologic therapy for patients exhibiting life-threatening propranolol or atenolol toxicity includes the combination of intravenous fluids, inotropic agents (e.g. dobutamine, dopamine and noradrenaline), phosphodiesterase inhibitors, and/or glucagon. Glucagon is the first line agent for hypotension and heart failure associated with beta blocker toxicity. Bypassing the β receptor, glucagon enhances myocardial contractility by stimulating adenyl cyclase. This increases cyclic AMP levels and intracellular calcium flux, resulting in positive inotropic and chronotropic effects. Glucagon is given as a 2-10 mg bolus (50-150 mcg/kg), followed by continuous infusion of 1-5 mg/h, as dictated by the clinical response. The large dose of glucagon required for myocardial action may result in nausea, transitory vomiting, and moderate hyperglycemia. Clinicians using glucagon for this indication should assure themselves that the diluent used to reconstitute the hormone does not contain phenol.

In the canine model of beta blocker poisoning, amrinone, a phosphodiesterase inhibitor, has been shown to possess a positive inotropic effect similar to glucagon. Unlike glucagon, amrinone failed to improve propranolol-induced bradycardia. Combined treatment with glucagon and milrinone yielded no additional benefits in a canine model.

Atropine inhibits the vagal drive to the heart by blocking the action of acetylcholine at muscarinic receptors. Though atropine was described as the most frequently drug used in the treatment of beta blocker toxicity, it is also the least effective. As for inotropic agents, it is very difficult to predict the dose of agonist required to overcome the effect of an overdose with a particular beta blocker. The only practical approach is to initially start with the recommended dose of a particular agonist and the increase the dose to clinical response.

The efficacy of a novel antidote, insulin and glucose was tested against the standard treatment of glucagon and epinephrine in a canine model. Results showed that animals administered glucose and insulin had a greater survival compared with standard treat-ment. The proposed efficacy for insulin and glucose in beta blocker toxicity includes an enhanced catecholamine release, increased myocardial substrate use, and altered calcium homeostasis. In experimental models, insulin was given at a dose of one unit/kg per hour intravenously; a solution of 10% dextrose is given to maintain euglycemic levels in the blood. Nonetheless, this is only one experimental animal study and is yet to be replicated or studied in humans. Its clinical applicability to the management of poisoned patients is presently unknown.

In a case report, calcium chloride was successfully used to treat hypotension from atenolol poisoning refractory to glucagon and epinephrine. Calcium chloride is thought to improve depressed hemodynamic status mainly by positive inotropic action.

Though a temporary pacemaker could be used to treat beta blocker induced bradycardia, reports of failure to improve clinical status in serious overdose despite the use of pacing are common.

In conclusion, 30% to 40% of beta blocker intoxications can be asymptomatic but the mortality can be as high as 26% for propranolol poisoning cases. Fortunately, prognosis is improved if appropriate treatment is initiated early.

References: