Title: CONTINUOUS PROPRANOLOL INFUSION; ISOPROTERENOL RESPONSE

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In the postoperative period it is desirable to attenuate heightened sympathetic activity in patients with coronary artery disease to avoid associated increases in myocardial oxygen demand. Propranolol (P) is used in small intermittent intravenous boluses for this purpose. However, a continuous intravenous infusion of propranolol (CIP) has been shown to provide stable, predictable plasma levels based on pharmacokinetic data.[1] This study examined the efficacy of CIP in providing ß-adrenergic blockade as determined by heart rate (HR) responses to isoproterenol (I).

Methods: Five patients (43-61 yrs) scheduled for coronary artery bypass surgery gave informed consent to this postoperative study which was approved by the Human Investigations Committee. Other than coronary artery disease, the patients had no significant illness and were taking medications limited to the treatment of angina pectoris. All had normal ventricular function (ejection fraction >0.5, end diastolic pressure <15 mmHg). They were taking P (92 ± 22 mg/day) and received their last dose at 10 pm the night before anesthesia (morphine, diazepam, pancuronium ± enflurane) and surgery (8 am). Following postoperative stabilization in the ICU, a control I dose-response test (IRT) was performed. This technique provides a means of assessing ß-adrenergic blockade and involves the administration of increasingly larger bolus doses of I until a HR increase of 25 bpm occurs.[2] HR is allowed to return to control between each dose. Three 1 mg boluses of P then were given as a loading dose and CIP started at 0.7 µg/kg/min and continued for 3 hours. IRT were begun at ½ and 2 hours during P infusion. Blood samples were taken before and after induction of anesthesia, following cardiopulmonary bypass (CPB), prior to the first IRT, and every 15 min for the first 2 hr of CIP and every ½ hr thereafter. Plasma was separated from blood and analyzed for P. Linear regression analysis was used to compare the HR response to the 3 IRT in each subject. $P<.05$ was significant. Results are expressed as mean ± SE.

Results: The three 1 mg IV bolus doses provided a rapid increase in P concentration from intraoperative levels (Fig 1). Predicted steady state P levels based on a clearance of 1.2 l/kg/hr and an infusion rate of 0.7 µg/kg/min was 35 ng/ml which corresponded to observed levels. This P level produced a significant shift in the dose-response curve (Figure 2). For an increase in HR of 20-25 bpm, there was a 3-4 fold shift to the right. The responses ½ and 2 hours following initiation of CIP were not significantly different.

Discussion: Plasma P concentrations of 14 to 90 ng/ml have been shown to provide optimal relief of angina pectoris with a 64-98% blockade of exercise-induced tachycardia. We rapidly achieved levels in this range with a 3x1 mg IV loading dose. The concentration was maintained effectively by CIP and approximated predicted values. The tendency of P concentrations to rise agreed with previous results requiring >3 hrs for steady levels to be achieved. The pharmacological efficacy of P levels obtained by CIP was represented by a significant shift in HR response to I. The slight change in levels between ½ and 2 hours did not affect response and indicated a stable ß-adrenergic block. In summary, the stable pharmacological effect provided by CIP suggests this to be an effective means of providing intravenous ß-adrenergic blockade therapy.

References:
1. Wells PH., Hug CC, Jr., Kaplan JA: Maintenance of propranolol therapy by IV infusion. Anesthesiology 51: s111, 1979.
2. Cleveland CR, Rangno RE, Shand DG: A standardized isoproterenol sensitivity test. Ann Intern Med 130: 47, 1972.