Title: PROPRANOLOL AND THE DISSOCIATION CURVE

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Introduction. Propranolol in large doses, in vitro, has been shown to shift the oxyhemoglobin dissociation curve to the right.[1] The therapeutic effect of propranolol in the anginal syndrome has been postulated to be partially dug to increased myocardial tissue oxygen delivery.[2] Human blood exposed to clinical doses of propranolol has not been studied under the rigid controls necessary to accurately interpret changes in the oxyhemoglobin dissociation curve.

Methods. A 50ml venous blood sample was drawn from 14 healthy non-smoking hospital employees. Hematocrit, hemoglobin, hemoglobin electrophoresis, and 2,3-disphosphoglycerate concentrations were measured on each sample. Propranolol treated aliquots were compared to a control aliquot in duplicate samples while exposed to 4.0 or 5.9% oxygen in 6% carbon dioxide with the balance nitrogen. Propranolol dosage was calculated from the expected level in blood, assuming equal whole body distribution, after an intravenous dose of 3.5mg, 35, and 140mg. Each sample was individually tonometered, analyzed, and PO_2 valves corrected to pH 7.40 at hemoglobin saturations in the linear portion of the dissociation curve.[3] Temperature was controlled at 37°C and $paCO_2$ at 40mmHg. Control and propranolol-treated samples were statistically compared using a paired t-test.

Results. Hematocrit, hemoglobin, and 2,3-DPG valves were normal. Hemoglobin A was found in all blood samples. After PO_2 corrections were completed, two-point saturation curves were plotted for each control and drug treated sample. A PO_2 for hemoglobin saturation at 62% (P62) and 68% (P68) was read from the saturation curve for each sample and used for accurate comparisons. Clinical blood concentrations (0.71ug/ml, 7.1ug/ml, and 28.6ug/ml) of propranolol did not significantly alter the position of the oxyhemoglobin dissociation curve.

Discussion. Propranolol has gained widespread use in the therapy of angina, hypertension, cardiac dysrhythmias, and migraine headaches. Large doses (100ug/ml plasma) of propranolol in vitro have been shown to cause ionic shifts in the red cell with plasma potassium rises from 4 MEQ/L to 26 MEQ/L. This ionic shift alters the Gibbs-Donnan equilibrium balance of the red cell causing a shift in the hemoglobin dissociation curve secondary to the classic Bohr effect seen with an increase in the hydrogen ion concentration.[4] Studies with oxyhemoglobin dissociation curves require meticulous attention to detail. The present study reveals that propranolol does not alter the hemoglobin dissociation curve in doses of 3mg to 140mg intravenously. In clinical settings the effacious action of propranolol is not due to any effect on the oxyhemoglobin dissociation curve but related to the Beta-blocking capabilities.

References.

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3. Petty C, Bageant: The effect of morphine, meperidine, fentanyl, and naloxone on the oxyhemoglobin dissociation curve, J Pharmac Exp Thera 190: 176-179, 1974
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	Concentration ug/ml	P62	P68
Control		31.6±0.4*	35.0±0.4
Propranolol	0.71	31.0±0.9	34.9±0.7
Control		31.5±0.4	35.0±0.4
Propranolol	7.1	31.0±0.3	34.8±0.2
Control		31.5±0.4	35.0±0.4
Propranolol	28.6	31.4±0.1	34.7±0.3

*Mean ± S.E.

Effect of propranolol on oxygen tension at P62 and P68 at pH 7.40, 37°C, and 40mmHg $PaCO_2$.