TITLE: Effects of Aminophylline on Pulmonary Vascular Resistance

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INTRODUCTION: The postoperative morbidity and mortality following mitral valve replacement seems to be related, at least in part, to the existence and persistence of an increased pulmonary vascular resistance (PVR). Although several vasodilator drugs have been shown to be effective in this setting, we are not aware of a quantification in terms of effective plasma concentrations of aminophylline, a drug that combines several desirable qualities for postoperative use, i.e., vaso- and bronchodilatation, myocardial inotropy and stimulation of urine flow.

METHOD AND MATERIAL: Informed consent was obtained from six patients, ages 21 to 59 years, admitted with the clinical diagnosis of predominant mitral stenosis. Preoperative right and left heart catheterization demonstrated moderate to severe mitral stenosis with PA pressures at rest of > 65/20 torr and further elevation during exercise; PCW pressures at rest of > 20 torr which increased further during exercise; cardiac indices at rest of < 2.5l/min/$m^2$ and no increase during exercise; a negative coronary angiogram; and no significant left ventricular wall motion abnormality. The appropriate monitoring lines were inserted prior to induction of anesthesia in the operating room. The patients were ventilated throughout the study with a volume-controlled ventilator. All patients were paced sequentially at the end of the operation at 90-110 beats/min. 12 h. after the operation, theophylline was administered through a constant infusion pump at a rate of 70 µg/kg/min for 30 min followed by 140 µg/kg/min for the next 30 min. All hemodynamic measurements were recorded before the start of the infusion, then every 15 min during and 1 h. after the end of the infusion. Simultaneously, samples were drawn and plasma concentrations of theophylline were measured by UV spectrophotometry. All samples were analyzed in duplicate and had coefficients of variation of less than 8%.

RESULTS: Plasma concentrations of theophylline obtained during the study are shown in Table 1. At two consecutive plasma concentrations of 5.4 µg/ml and 11.8 µg/ml theophylline, only mean PA pressure and PVRI decreased significantly ($p < 0.001$) from control. CI and SVRI remained unchanged. The effect of theophylline on the pulmonary circulation is shown in Table 2. Changes in PVR appear at low plasma concentrations. This correlation suggests that the mode of action of theophylline on the pulmonary vasculature is similar to its action on smooth muscle. Side effects appeared in the following sequence: during the first half-hour of the study, the patients became more alert and increased their respiratory rate. Ten to 20 min after the start of the 140 µg/kg/min infusion, most patients complained of nausea. In one patient, heart rate increased beyond the pacing rate and ventricular arrhythmia appeared at the end of the 140 µg/kg/min.

CONCLUSION: Following MVR, theophylline decreased pulmonary vascular resistance in a concentration-dependent manner. In the absence of facilities for measurement of plasma concentrations, we propose an initial loading dose of 70 µg/kg/min for 30 min, followed by 140 µg/kg/min until the appearance of side effects. This appears to be required in order to obtain a reduction in PVR to 66% of control values.

Table 1

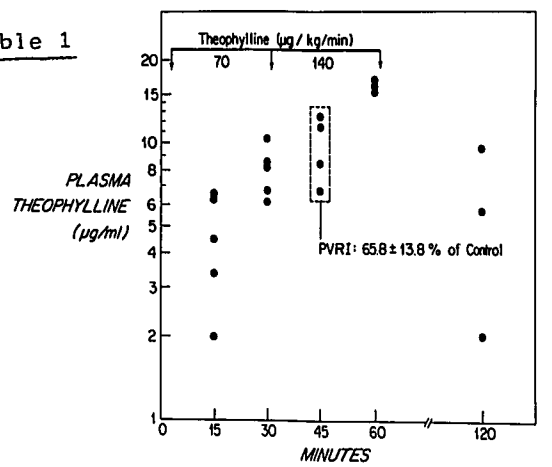


Table 2

RELATIONSHIP BETWEEN PLASMA THEOPHYLLINE CONCENTRATION AND PULMONARY VASCULAR RESISTANCE INDEX