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ORCIPRENALINE DOES NOT ALTER THEOPHYLLINE ELIMINATION

Theophylline is a widely used bronchodilator which has a narrow therapeutic index. Achieving and maintaining therapeutic but nontoxic serum levels of the drug may be difficult because many factors can alter theophylline disposition and elimination. Cigarette smoking and ingestion of charcoal broiled foods enhance theophylline metabolism; heart failure, liver disease and ingestion of propranolol and macrolide antibiotics reduce theophylline elimination (Ogilvie, 1978; Conrad & Nyman, 1980). Many patients require sympathomimetic drugs in addition to theophylline to control symptoms of bronchospasm. Since β -adrenergic receptor blockade with propranolol and metoprolol reduces theophylline metabolism, we were concerned that β -adrenergic receptor stimulation might have the opposite effect. In this study, we have investigated the effect of administration of the commonly used β -adrenergic receptor agonist, orciprenaline (metaproterenol), upon theophylline elimination.

This study was done in six male volunteers, aged 22 to 29 years. Informed consent was obtained from each subject according to the guidelines established by the Human Subjects Committee of the University of Arizona. Each subject was judged to be healthy after a medical history, physical examination and laboratory tests including blood chemistries and electrocardiography were completed. None of the volunteers smoked cigarettes and none ingested excessive amounts of methylxanthine containing foods or beverages.

Aminophylline (equivalent to 5.1 mg/kg theophylline) (Aminophylline injection, Elkins-Sinn) was given intravenously through an indwelling catheter in a forearm vein over a period of 30 min. Three infusions were given: first, without concomitant medication; second, 2 h after ingestion of orciprenaline sulphate 20 mg (Alupent, Boehringer Ingel-

heim) which was given orally every 8 h for 3 days before and during the day of aminophylline administration; third, 2 h after inhalation of three puffs, each containing 0.65 mg, of orciprenaline aerosol (Alupent metered dose inhaler, Boehringer Ingelheim) which was given four times a day for 3 days before and during the day of aminophylline administration. The dose intervals for orciprenaline are those recommended by the manufacturer, and were designed to achieve steady-state effects of orciprenaline by the time that aminophylline was given. Dietary methylxanthines were prohibited for 24 h before aminophylline was given. Each study was separated from the subsequent one by a period of 14 days; the sequence of the studies was randomized.

Blood was obtained through a catheter placed in the forearm contralateral to the infusion site before and at 1, 2, 4, 7, 10, 13, 16, and 24 h after aminophylline administration. The blood was collected in a vacutainer tube which contained no anticoagulant. The sample was refrigerated and centrifuged as soon as possible after collection. The serum was placed in a polyethylene tube, frozen at -20°C , and assayed for theophylline within 1 week. Theophylline serum concentrations were measured using a modification of a gas-chromatographic assay (Perrier & Lear, 1976). This assay was sensitive to theophylline serum concentrations as low as $0.1\text{ }\mu\text{g/ml}$. The coefficient of variation of the assay was 5.1% at theophylline concentrations of $15\text{ }\mu\text{g/ml}$, 5.0% at $10\text{ }\mu\text{g/ml}$, and 5.6% at $5\text{ }\mu\text{g/ml}$.

Immediately before aminophylline was administered, the heart rate (without orciprenaline) was 69 ± 11 beats/min. During the orciprenaline inhalational period, the heart rate was 71 ± 13 beats/min, not significantly different from the 'control' period. When orciprenaline was given orally, the heart rate was 83 ± 17 beats/min ($P < 0.001$ v control). Neither

the systolic nor the diastolic blood pressure were changed by orciprenaline.

Orciprenaline produced no significant differences in theophylline disposition. Theophylline clearance (measured by dividing the dose by the theophylline AUC) was $0.047 \pm 0.009 \text{ l kg}^{-1} \text{ h}^{-1}$ before orciprenaline, $0.045 \pm 0.008 \text{ l kg}^{-1} \text{ h}^{-1}$ during oral orciprenaline, and $0.046 \pm 0.009 \text{ l kg}^{-1} \text{ h}^{-1}$ during inhalational orciprenaline. The elimination rate constant was $0.086 \pm 0.012 \text{ h}^{-1}$ before orciprenaline, $0.086 \pm 0.020 \text{ h}^{-1}$ during oral orciprenaline, and $0.087 \pm 0.020 \text{ h}^{-1}$ during inhalation of orciprenaline. The volume of distribution of theophylline was $0.551 \pm 0.071 \text{ l/kg}$ before orciprenaline, $0.542 \pm 0.120 \text{ l/kg}$ during oral orciprenaline, and $0.543 \pm 0.078 \text{ l/kg}$ during inhalation of orciprenaline.

This study shows that doses of orciprenaline which are commonly used clinically do not alter the disposition of single acute doses of intravenously administered aminophylline. This is in agreement with a

previous report which showed that orciprenaline produced no change in theophylline concentrations in asthmatic children (Rachelefsky *et al.*, 1980). There should be no need to alter theophylline dosage if orciprenaline is coadministered in doses similar to those we have studied.

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