PULMONARY EXTRACTION OF N-ISOPROPYL-I-123-p-IODOAMPHETAMINE IN THE PRESENCE OF PROPANOLOL USING DUAL INDICATOR DILUTION TECHNIQUE

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ABSTRACT

In order to determine the sensitivity of the procedure for detecting and measuring pharmacological intervention in the pulmonary endothelial amine receptors, propranolol was administered intravenously to the intact dogs at different dose levels. Pulmonary extraction of N-Isopropyl-I-123-p-Iodoamphetamine (IMP) with and without pharmacological intervention was determined by the rapid sequential imaging, following the intravenous injection of a reference tracer and later a test tracer. Input vascular and organ time-activity curves were obtained. The input vascular and organ curves of the reference tracer were gamma fitted and were deconvolved. Predicted residue function for the test tracer was determined by convolving the input vascular curve of the test tracer with the impulse response function of the reference tracer under stable physiological conditions. The calculated first pass pulmonary extraction values of IMP in the pretreated dogs with propranolol given ten minutes prior to the reference tracer in the dose of 1, 3, 5, 10, 15 and 20mg were 0.81, 0.77, 0.71, 0.62, 0.62, and 0.62 respectively, relative to Tc-99m dextran as a reference tracer, whereas the normal IMP first pass pulmonary extraction was 0.90 ± 0.03. Uptake of IMP may provide a sensitive probe with which to detect and evaluate the physiological interaction of pulmonary endothelial cell in a clinical environment using a noninvasive procedure.

INTRODUCTION

In addition to its major role as the organ of external gas exchange the pulmonary circulation in the lung also serves as a metabolic regulator of substances circulating in the blood. Evidence suggests that the lungs can remove and deactivate circulating vasoactive amines; many substances that act on the vascular or central nervous system, including norepinephrine, serotonin, prostaglandin, and bradykinin, are selectively removed by the endothelial cells of the lungs. (1) Analyses of the metabolic functions of the lung, especially the lung's effect on the concentration on circulating bioamines such as amphetamine and other amines have opened a new vista of lung research into the study of the metabolic functions, mechanism of extraction and physiological perturbation.

The potential for using gamma emission imaging technique to visualize metabolic processes of the lung has been studied by other investigators. Fowler et al (2) have demonstrated the potential of C-11 Octylamine in vivo as a diagnostic agent for the lung structure and function in rabbits. Gallagher et al (3) using C-11 Octylamine in humans, showed an initial high uptake in the lungs. Syrota et al (4) have reported uptake of C-11 chlorpromazine in human lungs. Rahimian et al (5) have reported a high lung uptake of N-Isopropyl-I-123-p-Iodoamphetamine (IMP) in the dogs. In this report, attempts are made to clarify the mechanism of IMP uptake with other amine pharmaceutical (propranolol) that has been studied in considerable detail by other investigators. Competitive interaction between IMP and propranolol indicates that the invivo procedure has enough sensitivity to measure drugs and metabolic interactions in the lung receptors. The feasibility of such procedure will enable to study pulmonary physiology in health and disease.

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MATERIALS AND METHODS

Four dogs were used in both control and experimental studies. The dogs weighing 17 to 20 kg were anesthetized with an intravenous dose of the short acting barbiturate, thiamylal, approximately 15 minutes prior to injection of the reference tracer. These dogs were free of known diseases and were provided a week of rest, before being used in any of the present studies. No medication was administered to the dogs during this time.

The dual indicator dilution technique was used to study the effect of the pulmonary extraction of IMP with and without the influence of pharmacological intervention of propranolol. A 3 to 4 mCi of Tc-99m dextran (reference tracer) was followed by a bolus of 3 to 4 mCi of I-123 IMP (test tracer). The competing substance propranolol was injected 10 minutes prior to the reference tracer. The same injection site and technique were used for each bolus. 20% windows were used at 140 KeV for Tc-99m and at 159 KeV for I-123.

The distribution of radioactivity in different organs

invivo was continuously monitored with a large field of view (LFOV) scintillation camera. The camera was interfaced with a PDP 11/40 computer. Information generated was recorded in 64 x 64 matrices. The frame mode resolution time was 4 frames per second for 25 seconds.

DATA ANALYSIS

Dual indicator dilution technique was used in this study. The reference vascular system, the test tracer (IMP) whose extraction was to be determined. Separate injections of tracers under stable physiological conditions were employed in this study.

Right heart and lung time-activity curves generated for each individual administered tracer and were corrected for background. Time-activity curves of the right heart and lung for the reference and test tracers were fitted with a gamma variate of the form

$$R(t) = K\, t^{\alpha} e^{-t/\beta} \qquad (1)$$

Where t = time after injection

$R(t)$ = radiotracer concentration at time, t

K = constant scale factor

α, β = are the arbitrary parameters determining the shape of the curve

Gamma variate fits of the right heart and pulmonary curves were deconvolved to yield the pulmonary response function of the reference vascular tracer. The gamma variate fit to the right heart curve for the test tracer is then convolved with the pulmonary impulse response function of the reference tracer to yield a predicted pulmonary vascular curve for the test tracer. The observed and predicted curves for the test tracer were normalized by their respective peak values and are plotted as the residue functions of the actual and predicted test tracer (Fig. 1). The extraction was calculated using the equation

$$E(t) = \frac{R_T(t) - R_R(t)}{1 - R_R(t)} \qquad (2)$$

Where $R_T(t)$ and $R_R(t)$ are the normalized residue functions following an impulse injection for the test and reference tracer. When the injection is very short, $R(t)$ can be considered to be equal to $C(t)/C(0)$, where $C(t)$ is the count rate of isotope emissions detected at time 't' and $C(0)$ is the peak observed immediately after injection. Therefore, the residue function $R(t)$ assumes fractional values between 0 and 1.0 of the administered dose.

RESULTS

In this study, the pulmonary extraction fraction of IMP was determined four times in four dogs. Fig. 1 shows the residue function $R(t)$ of the predicted IMP and the observed IMP from which the extraction was taken at the time when the lung curve of the reference tracer had descended to 30% of its peak value. (Fig. 2) The extraction fraction for IMP is 0.90 ± 0.03 when no competing substance was injected. This result is in confirmity with our previous result (4).

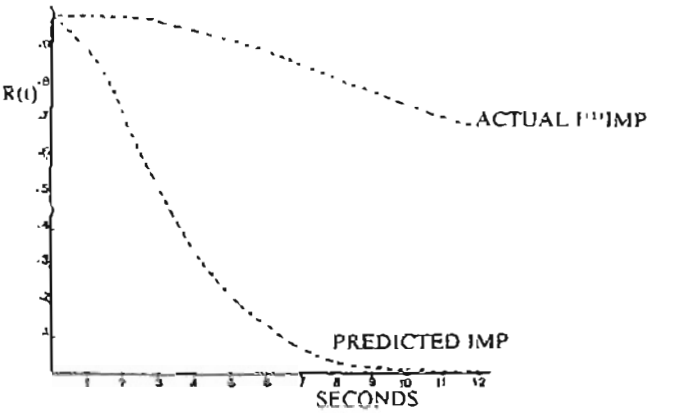

Figure 1: Residue functions for IMP, and predicted vascular curve. The curves are normalized to their respective peaks values and then shifted to time zero.

After pharmacological intervention with propranolol, however, different extractions were determined. In 15 experiments, 1, 3, 5, 10, 15, and 20 mg of propranolol were given intravenously 10 minutes prior to the adminstration of reference tracer. The first pass pulmonary extraction ratio of IMP were 0.81, 0.77, 0.71, 0.62, 0.62, and 0.62 respectively (Fig. 3).

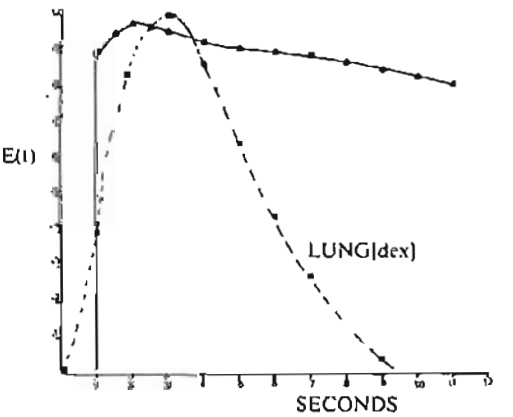

Figure 2: Extraction function for IMP, using equation (2). Extraction was taken at the time when the lung curve of the reference tracer had descended to 30% of its peak value.

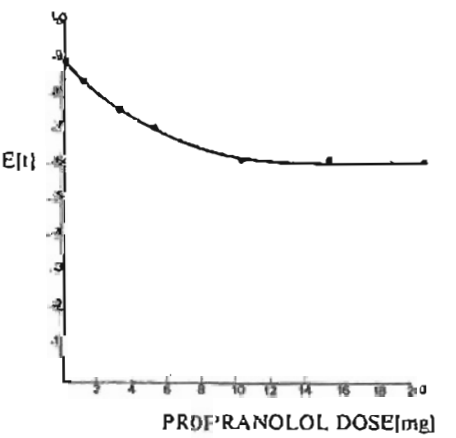

Figure 3: Pulmonary extraction of IMP following propranolol administration at different dose levels.

DISCUSSION

Metabolic lung functions are interrelated having at least a common anatomical place in the pulmonary endothelium. The uptake of active metabolites is done by specific receptors in the endothelial membranes. The assessment of these receptors in normal and pathological conditions is an important step to progress in our knowledge of the lung metabolic functions.

Primary biogenic amine clearance is a carrier-mediated drug sensitive process linked with uptake into endothelial cells and subsequent breakdown by monoamine oxidase and other enzymes (6). Lung endothelial receptors, on the other band, have an active role in the modulation of the neurotransmitter and vasoactive amines. D-amphetamine specifically binds to pulmonary endothelial amine receptors and IMP behaves very similar to D-amphetamine (7). The high turn over of IMP in the lung indicates that the procedure has enough sensitivity to measure receptor-mediated metabolic functions of the lung. The first pass pulmonary extraction of IMP in the control dogs was 90 ± 3%. This result is in confirmity with Syrota et al (4) and Gillis et al (8) using C-11 chlorpromazine (CPZ) and 5HT in human lungs reported 90% extraction. Rahimian et al (5) also reported 92% extraction of IMP in normal dogs. In order to further evaluate the method for detecting and measuring pharmacological intervention in the pulmonary endothelial amine receptors; propranolol was chosen as an investigative drug for the pharmacological intervention with IMP.

Experimental and clinical applications of IMP to the study of pulmonary endothelial pathophysiology requires quantitative techniques for measuring its uptake in the lungs, and also demonstrating the competitive effect of beta adrenoceptor antagonists for the binding sites of IMP in the pulmonary blocker. Propranolol inhibits both β^1 and β^2, leaving alpha untouched. Mammalian lungs have enormous ability to concentrate propranolol and Pang et al (9) pointed out that up to 94% of propranolol being removed from the pulmonary circulation in a single passage. However, the precise ways and means of propranolol uptake in the lung is not been known yet with absolute certainty (10).

Metabolic studies of propranolol indicates that at least 90% of the activity is taken up into the lung slices during a 30 minutes incubation with a labeled propranolol and is accounted for the parent compound itself (11). It has been also concluded that little or no metabolism of propranolol ocurred during this period. Similar findings was reported by Dollery et al (12) in the perfused rat lung using perfusion times of up to 10 minutes. Geddes et al (13) reported that 75% of injected propranolol was taken up by the lungs of concious patients.

Under the influence of general anesthesia, propranolol uptake after a single passage through the canine pulmonary circulation in vivo was greater than in concious dogs (14). The decrease in cardiac output in the anesthetized dogs may be linked with an enhanced transit time through the lungs, which in turn exposed the pulmonary endothelium for a longer period by the injected propranolol, since the uptake of the drug is thought to occur in endothelial cells (15). The longer time of exposure, should result in higher turnover of propranolol in the lung. However, change in cardiac output may not be the only explanation since no correlation was found between propranolol uptake and the cardiac output in concious dogs (16), although, the range of the cardiac output was less in an anesthetized dogs.

The high turnover of propranolol in the lungs may be due to its high lipid solubility. This contention is supported by a positive correlation between the degree of lung uptake and the log partition coeffecient of β-adrenoceptor antagonist between octonol and buffer (17). Most likely explanation of propranolol uptake in an anesthetized dog is that anesthetic agents interacts with the endothelial cell membrane and facilitates the uptake of the lung.

The first pass pulmonary uptake of IMP may be a useful index of probing endothelial cell function. However, it can be disputed that the IMP taken up by the lung will not be taken up mainly by the endothelial cell function. However, it can be the most logical assumption to assume that the pulmonary endothelium is the major site of uptake under the time scale of the first pass is very brief and pulmonary endothelial cells are the first one to encounter by administered IMP.

The extraction of the IMP were inhibited as the dose of propranolol increases as shown in Fig. 3 Competitive inhibition is the most likely mechanism of inhibited IMP uptake in the lungs. This is due to the fact that propranolol share the same route as that of IMP. Geddes et al (13) have reported that human patients already on propranolol medication showed less lung uptake of the intravenous dose of propranolol.

The first pass IMP pulmonary extraction ratio was 62% under influence of 10 mg of propranolol, whereas 15 and 20 mg of propranolol dose given 10 minutes prior to the reference tracer revealed the same extraction ratio. In this case, attempts have not been made to go beyond 20 mg of propranolol because of the risk of severe depression of cardiovascular function.

The 62% first pass pulmonary extraction of IMP in the presence of propranolol obtained in this study can be compared with the first pass pulmonary extraction of IMP in the presence of ketamine. The first pass pumonary extraction of IMP in the presence of ketamine was 64% (5). This is due to active competition for similar binding sites. Furthermore, in the chronic obstructive lung disease, pulmonary extraction was 64% using C-11 CPZ (4). The results suggest that the pulmonary uptake of IMP may be at least partially

mediated by receptors. Furthermore, studies of the degree of lung uptake may be a useful index of pathologic states in which alteration of amine receptors have occurred. In addition to this, uptake of IMP may provide a sensitive probe with which to detect and evaluate the physiology of competitive pharmacological intervention of pulmonary endothelial cell in a clinical environment using a non-invasive procedure.

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