Pulmonary Extraction of C-11 Chlorpromazine, Measured by Residue Detection in Man

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Uptake of C-11 chlorpromazine (CPZ) was measured to evaluate the nonrespiratory function of lung in patients. A multiple-indicator dilution technique was used with external detection. Following intravenous bolus injection of C-11 CPZ, with In-113m transferrin as an intravascular reference molecule, counts were recorded with a scintillation camera using two energy windows. The residue functions, R(t), for C-11 CPZ and In-113m transferrin were plotted against time for selected areas of interest, and the CPZ area-weighted extraction, E(t), was computed for the same areas every 250 msec using the formula: $E(t) = [R_T(t) - R_R(t)]/[1 - R_R(t)]$, where R_T and R_R are the normalized residue functions for CPZ and transferrin, respectively. The initial extraction was 90 ± 5% in four normal subjects and 64 ± 7% in six patients with chronic obstructive lung disease (C.O.L.D.), these values being significantly different ($p < 0.001$). The large initial extraction of CPZ in a single passage through the pulmonary vasculature resulted from a fixation to membranes, due to its high liposolubility. The lower extraction seen in patients with C.O.L.D. was explained by weaker fixation to lung tissue.

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It is now recognized that in addition to the function of gas exchange, the lungs have important nonrespiratory functions. Lungs are capable of removing and degrading several important circulating vasoactive hormones including biogenic amines (*1*). It is only recently that any appreciable attention has been given to the pulmonary accumulation of inhaled and circulating xenobiotics (*2*). Numerous enzymes, not very different from those found in liver, are located in the epithelial and the endothelial cells (*3*). Studies using isolated perfused lungs have shown that many basic chemicals accumulate with high tissue-to-blood ratios. It has been demonstrated that the basic amines chlorpromazine and imipramine have several types of binding sites, some of which are specific and others nonspecific (*4*).

Measurement of the uptake of molecules, such as chlorpromazine (CPZ), in humans allows the assessment of this nonrespiratory function. In order to evaluate pulmonary cell function in a noninvasive manner, we have developed a method using external detection, based on the principles of the multiple-indicator dilution technique (*5*). This involves a bolus injection of C-11 chlorpromazine and In-113m transferrin followed by the recording of pulmonary activity with a scintillation camera. Since transferrin did not cross the capillary barrier in a single passage, it could be considered as an intravascular reference tracer. Pulmonary extraction of C-11 CPZ from the blood was calculated in normal subjects and in patients with obstructive lung disease.

MATERIAL AND METHODS

Ten patients were studied: four had no pulmonary disease and six had chronic obstructive lung disease (C.O.L.D.) as assessed by clinical, radiological, and functional tests.

A method for synthesizing C-11 CPZ by the action of C-11 formaldehyde on nor-CPZ has been described

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previously (*6*). A specific activity of 300–500 mCi/μmol C-11 CPZ was obtained, with a radiochemical purity of 100%.

The patients, in a supine position, were injected intravenously with about 10 mCi of C-11 CPZ and 15 mCi of In-113m transferrin. Both agents, mixed together in 1 ml in a syringe, were injected as rapidly as possible through a catheter. The scintillation camera, fitted with a collimator designed for the 511-keV photons, was positioned over the patients' chests. An energy window of 20% was used for C-11 and one of 17% for In-113m. Acquisition was made in list mode, using these two simultaneous windows for 45 sec. Areas of interest were selected over the lungs based on radiological data; they usually included an entire lung because lesions were diffuse. The counts recorded in each 250-msec interval were plotted against time. The In-113m transferrin curve was corrected for Compton scatter from C-11 activity using a phantom. Both curves were normalized so that their peak values were set at 1 in order to represent residue functions, R(t). R(t) is the ratio of the number of counts detected in an area of interest at time t divided by the maximum number of counts corresponding to time 0. It was assumed that at time 0 all tracer molecules had entered the lungs but had not yet escaped.

CALCULATION OF EXTRACTION

Using conventional outflow detection, area-weighted extraction is obtained by (*7*):

$$E(t) = \frac{\int_0^t (C_R(\tau) - C_T(\tau))\, d\tau}{\int_0^t C_R(\tau)\, d\tau},$$

where C_R is the radioactive concentration of the reference vascular tracer (transferrin) and C_T the radioactive concentration of the test molecule (CPZ). Each C_R and C_T value is normalized by dividing the concentration at time τ by the amount of tracer injected and is expressed in ml^{-1} (*8*). This formula can be modified to calculate extraction from residual radioactive content of both reference and test molecules in the organ. For each tracer the amount of activity at any time is equal to the difference between the quantity injected into the lungs at time 0 and the quantity that has left the lungs between 0 and t (*8*).

$$R(t) = 1 - F \int_0^t C(\tau)\, d\tau,$$

where F is the pulmonary blood flow. The extraction formula is obtained from the residue functions: $E(t) = [R_T(t) - R_R(t)]/[1 - R_R(t)]$. Extraction of C-11 CPZ was computed for each area of interest.

RESULTS

Figure 1 shows the CPZ image formed in a normal subject using all events detected during 45 sec. No activity was seen in the heart or liver at this early time. Residue functions obtained following a bolus injection of both C-11 CPZ and In-113m transferrin are shown in Fig. 2. Lung activity increased rapidly and similarly for both agents. Washout of CPZ was much slower than that of transferrin. Curves of CPZ extraction against time are shown in Fig. 3 for the normal subject of Figs.

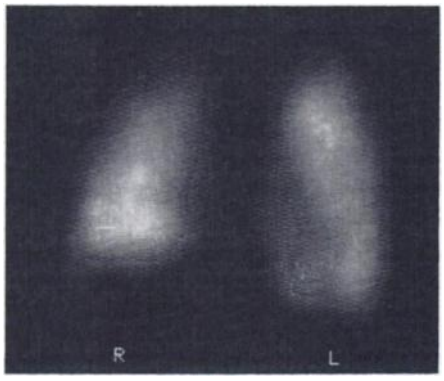

FIG. 1. Scan from normal patient following intravenous injection of C-11 chlorpromazine and In-113m transferrin. This corresponds to total of all events recorded for 45 sec in the C-11 window. Activity is seen in both lungs but not in liver.

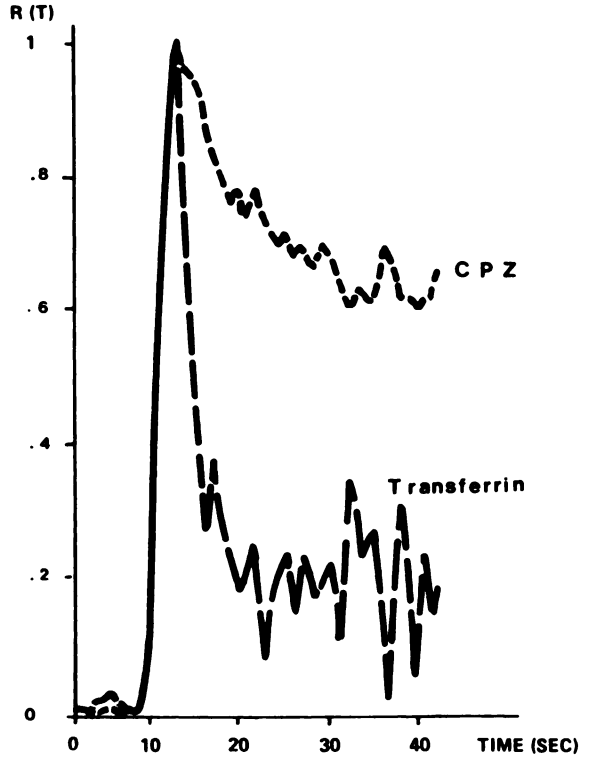

FIG. 2. Curves of residue function against time for C-11 CPZ and In-113m transferrin, recorded in an area of interest in right lung. Ordinate gives normalized number of counts recorded every 250 msec.

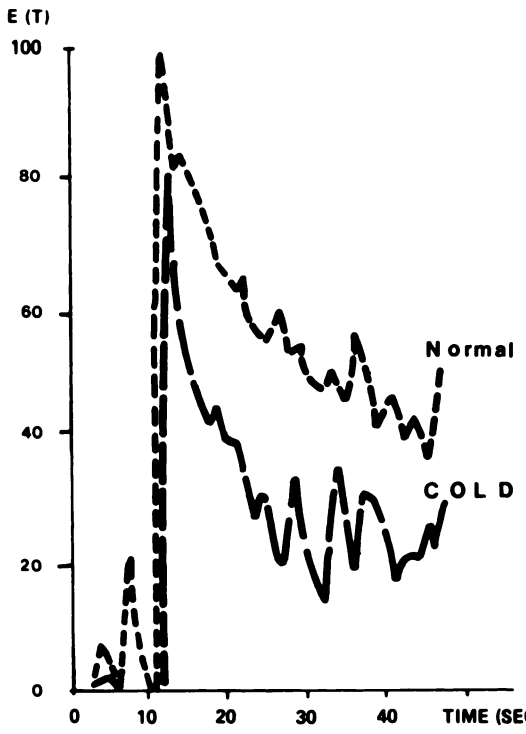

FIG. 3. Extraction of C-11 CPZ as function of time, calculated from residue functions obtained in one lung, for a normal patient and for one with chronic obstructive lung disease.

1 and 2 and for a patient with C.O.L.D. Extraction at time 0 is the initial extraction of CPZ in a single passage through the lung; it is also the maximum extraction. In the patients with C.O.L.D., maximum extraction (at time 0) is lower and it decreases more rapidly with time. Extraction at the 45th second is the value calculated at the end of data collection. It has a more complex meaning, reflecting mainly the importance of the back-diffusion of CPZ from the extravascular space to the blood. Values of extraction calculated at time 0 and at the 45th second are given in Table 1 for all the subjects studied. In normal subjects, the initial extraction, E(0), was 89.8% (mean); in patients with C.O.L.D. it was (63.5 ± 7.2)%. These means were significantly different ($p < 0.001$). The extraction calculated at 45 sec was 63.3% (mean) in normal subjects and (27.5 ± 7.8)% in patients with C.O.L.D., these values also being significantly different ($p < 0.001$).

TABLE 1. VALUES OF INITIAL EXTRACTION, E(O), AND EXTRACTION AT 45th SECOND, E(45)

Normal subjects			Chronic obstructive lung disease		
Pt.	E(O)	E(45)	Pt.	E(O)	E(45)
GO	87	54.5	BO	56	13
TS	97	55.5	LE	56.5	29
PE	85	79.5	LH	60	35
KA	90	63.5	LA	73.5	25.5
			BA	70	30
			OW	65	32.5
Mean	89.8	63.3	Mean	63.5	27.5
			s.d.	7.2	7.8

DISCUSSION

Until now, almost no one has investigated the non-respiratory function of the lungs in patients with lung disease, although a method of measuring pulmonary 5-hydroxytryptamine clearance was recently developed (*9*). This method is also based on a multiple-indicator dilution technique, but blood samples must be withdrawn from catheters inserted in the left atrium in anesthetized patients or in the radial artery in conscious patients. The metabolisms of 5-HT, phenylethylamine, prostaglandin E_2, and arachidonic acid have also been studied in samples of human lung obtained at operation and perfused through pulmonary vessels (*10*). Such techniques can be used only on patients who must be catheterized for other reasons; thus these invasive studies can be performed in only a few patients. The C-11 labeling of substances removed from the blood by the lung has several advantages: external detection is possible due to positron emission; the short half-life of C-11 (20.4 min) means that 10–20 mCi can be injected; C-11 specific activity is considerably higher than that of C-14; and images and dynamic studies are possible using a scintillation camera or a positron-emission tomographic system. Potential use of C-11-labeled aliphatic amines for studies of lung metabolism in vivo has been investigated previously in mice (*11*). In healthy volunteers, C-11 octylamine uptake was monitored dynamically with the gamma camera for 30 min and lung accumulation was expressed as a percentage of the injected dose (*12*). The method we have developed for patients is a quantitative one that does not need any blood sample, and the principles of measuring extraction are similar to those of the multiple-indicator dilution technique (*5, 7*). Extraction of CPZ from the blood is measured during a single passage into the pulmonary vasculature and calculated by comparing the activity of CPZ with that of a vascular tracer. Because high count rates for less than a minute must be recorded in two energy windows, only a gamma camera, not a positron camera, can be used, although its sensitivity is low when equipped with a collimator designed for 511-keV photons. Transferrin labeled with In-113m is a convenient vascular tracer because it does not cross the capillary wall in a single passage and because the In-113m radiation, although energetic (392 keV), can be differentiated from that of C-11. The contribution of C-11 in the In-113m window was 30%. The formula used to calculate extraction from the residue functions obtained by external detection is identical to that for area-weighted extraction obtained

from measurements of radioactive concentration in venous blood draining the organ.

In work with preparations of perfused organs, instantaneous extraction, calculated at each time t, is measured more often than area-weighted extraction. Both extractions have conceptually the same meaning, but the area-weighted extraction curve plotted against time is smoother than the instantaneous extraction curve, and this is an advantage in external detection due to the fluctuations of counting rates. The choice of a basic amine, such as chlorpromazine or imipramine, to evaluate a nonrespiratory function of the lung results from several considerations. In isolated perfused lungs, it has been demonstrated that this kind of molecule is not metabolized during the first few minutes. It is readily extracted from the perfusate, with a very large tissue-to-medium ratio (between 14 and 150) depending on the specific activity of the injectate (*2, 4*). Studies with imipramine have shown that the uptake process is due to two mechanisms: a linear nonspecific component and a saturable component corresponding to specific binding sites (*13*). In a single passage only the nonspecific binding sites can be detected. Imipramine is loosely bound to these sites and two rates of efflux with short half-lives (18 and 58 sec) could be distinguished. The high initial extraction (90%) observed in normal patients can be compared with the initial uptake of C-11 octylamine, which is 65–70% of the injected dose (*12*). It probably results from the very high lipid solubility of these basic molecules: lipid solubility of CPZ is of the same order of magnitude as that of imipramine and is a thousand times that of ethanol or antipyrine (*14*).

The first important result obtained with this method is the finding that the maximum extraction is lower in patients with chronic obstructive lung disease: 64% instead of 90% ($p < 0.001$). This difference cannot be due to the existence of nonperfused zones in the areas of interest, since the extraction of CPZ is calculated by reference to an intravascular tracer. It might be explained by a weaker fixation to lipidic membranes due to qualitative and/or quantitative alterations of lung tissue.

The real importance of the nonrespiratory function in lung disease is questionable and requires further investigation. In isolated perfused rat lung, alterations of the endothelial cells by monocrotaline (*15*) or hyperoxia (*16*) causes a significant decrease in 5-hydroxytryptamine clearance. This clearance was not increased in anesthetized patients undergoing prolonged cardiopulmonary bypass (*9*). Our noninvasive technique should allow us to assess the predictive value of an abnormal extraction of different molecules labeled with C-11 in lung disease. Some of these are not metabolized (e.g., CPZ) and provide data concerning the number of lung cells; others are metabolized by some kind of cell, endothelial (i.e., 5-HT) or epithelial.

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