Distribution and Kinetics of Carbon-11-Cocaine in the Human Body Measured with PET

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The extent to which the toxic properties of cocaine are related to its accumulation in various organs is not known. This study investigates cocaine uptake in the human body using ^{11}C-cocaine and PET in 14 healthy males. The rate of uptake and clearance of ^{11}C-cocaine varied among organs: peak uptake occurred in the lungs at 45 sec, in the heart and kidneys at 2–3 min, in the adrenals at 7–9 min, and in the liver at 10–15 min. Half-peak clearances were 90 sec in the lungs, 10 min in the heart and kidneys and 22 min in the adrenals. Liver radioactivity plateaued 10–15 min after injection and remained constant thereafter (40 min). Lung radioactivity paralleled that of plasma. The average uptake at peak was 0.007% (s.d., 0.001) dose/cc in the heart, 0.014% (s.d., 0.002) dose/cc in the kidney, 0.014% (s.d., 0.002) dose/cc in the liver and 0.034% (s.d., 0.001) dose/cc in the adrenals. The significant accumulation of cocaine in human heart, kidneys, adrenals and liver could contribute to its toxicity.

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Cardiac toxicity is the most frequent complication of cocaine abuse. Cocaine use can trigger myocardial infarctions (*1,2*) or lethal cardiac arrhythmias (*3*). Both central (*4,5*) and peripheral mechanisms (*6*) are responsible for cocaine's cardiotoxic properties. The contribution of peripheral mechanisms has been well demonstrated, since cocaine can induce changes in coronary flow (*7,8*) as well as cardiac arrhythmias (*9*) in anesthetized dogs. Cocaine's peripheral actions involve the release of adrenaline and noradrenaline from the adrenals (*10*), inhibition of norepinephrine reuptake sites in myocardial tissue (*11*), and local anesthetic effects in myocardial cells (*12*). The sympathomimetic effects of cocaine could produce coronary vasoconstriction (*13*) and/or change cardiac stability by altering transmembrane ion fluxes (*14*). The local anesthetic properties of cocaine, which result from inhibition of sodium influx, could further interfere with cell conductance (*15*). The relevance of the direct effects of cocaine in the heart is emphasized by studies that propose that cocaine is directly toxic to the myocardium (*16*) and that its anesthetic properties in myocardial cells can trigger cardiac asystole (*17*).

The accumulation of cocaine in the human heart has not been investigated in vivo. Postmortem studies have shown that cocaine binds to muscarinic receptors in the human heart (*18*) and that in individuals who have died of cocaine overdose there is a significant amount of cocaine in the myocardial tissue (*19*). The extent to which release of epinephrine from the adrenals contributes to the cardiotoxicity of cocaine has not been investigated. This study directly measured the accumulation and kinetics of cocaine in the human heart, lungs, adrenals, kidneys and liver using positron emission tomography (PET) with tracer doses of ^{11}C-cocaine and complements a recent PET study of the kinetics and distribution of ^{11}C-cocaine in the human brain in vivo (*20*).

MATERIALS AND METHODS

[N-^{11}C-methyl]cocaine was prepared as described previously (*20*). Carbon-11-labeled methyl-iodide was prepared according to the method of Langstrom (*21*) and purged into a cooled (−42°C) solution of norcocaine (2 mg, obtained from the National Institute on Drug Abuse) in acetonitrile (0.3 ml), dimethyl formamide (0.16 ml) and dimethylsulfoxide (0.040 ml). The reaction vessel was sealed and heated in an oil bath (135°C) for 5 min. Water (1 ml) was added and the reaction mixture was purified by semi-preparative HPLC (silica gel, Ultrasphere-Si, 10 × 250 mm) using a solvent mixture consisting of acetonitrile: 0.004 *M* $(NH_4)_2HPO_4$ (70:30) and a flow rate of 6 ml/min. The retention time of norcocaine in this system was 10–11 min and the retention time of cocaine was 15–16 min. The solvent was evaporated from the fraction containing the labeled cocaine and the residue was dissolved in 3 ml of isotonic saline (USP) for injection. The total synthesis time was 35 min. Its radiochemical purity was greater than 98% as determined by thin-layer chromatography (silica gel plates, acetonitrile:water:ammonium hydroxide (con)-90:10:1). The specific activity (determined by HPLC) was typically 250–500 mCi per μmole at the time of injection.

PET Scanning Procedures

Fourteen human volunteers (male, age range 21–47 yr) were studied. Subjects were healthy nonsmoker controls with no history of cardiovascular disease or drug abuse. A complete physical

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and neurological examination was done to exclude physical illnesses. Quantitative urine analyses were performed prior to each PET scan to ensure that no psychoactive drugs had been used. The subjects were asked to stop any medications 48 hr prior to the study. The scans were obtained after intravenous administration of 6–10 mCi of ^{11}C-cocaine (7–13 μg cocaine per injection). Studies for heart, lung and liver were done on 10 subjects, and kidney and adrenal studies were performed on 4 of the subjects. Five of the cardiac and pulmonary subjects received two scans with a 2–3-hr time interval between doses. For one subject, the scans were obtained with no pharmacological intervention to assess the reproducibility of cardiac and pulmonary uptake of ^{11}C-cocaine between measurements. For four subjects, the second scan was done 40 min after the intravenous injection of 2 mg benztropine mesylate (*22*) to determine the extent to which uptake of cocaine in the heart represented binding to muscarinic receptors and/or dopamine transporters. For the adrenals and kidney scans, the subjects were scanned only once and measurements were obtained across the lower thorax.

PET scans were obtained using a whole-body, high-resolution positron emission tomograph (6 × 6 × 6.5 mm, 15 slices, Computer Technologies, Inc., CTI-931). An initial transmission rectilinear scan was obtained with a ring filled with ^{68}Ge to locate the position of the heart. Placement of the subject within the gantry was readjusted using the information from the rectilinear scan. An attenuation scan was then obtained to correct for attenuation in the emission scans. The emission scans were obtained immediately after injection of ^{11}C-cocaine and for 40 min thereafter. One-minute scans were taken for the first 10 min and 10-min scans were taken at 10, 20, and 30 min.

Arterial blood was sampled automatically (Ole-Dick, Denmark) every 2.5 sec for the first 2 min and then every minute from 2 to 5 min, and thereafter at 7.5, 10, 15, 20, 30, and 40 min. Each blood sampling tube contained 1 mg of sodium fluoride to inhibit plasma cholinesterases and was kept at 4°C until analysis. All samples were centrifuged to obtain plasma, which was counted. Duplicated samples at 1, 5, 10, and 30 min were assayed for the presence of unchanged labeled cocaine using a slight modification of the solid-phase extraction technique (*23*). Briefly, plasma was added to 1 ml of water with mixing and the entire sample was counted. This then was diluted to 5 ml with water and applied to and slowly eluted through a C-18 Sep Pak (Waters Inc.) that had been previously activated by rinsing with 5 ml of methanol followed by 5 ml of water. The Sep Pak was successively eluted with 5 ml of 20% methanol, 5 ml of 50% methanol and 6 ml of 100% methanol.

Circular regions in the images were selected directly from the long-axis view of the heart for three consecutive slices across the left atrium, the left ventricle, and the interventricular septum. In addition, three circular regions of interest were selected across the right lung, three across the liver and two across the left adrenals.

RESULTS

There was high uptake of radioactivity into the human heart after intravenous injection of ^{11}C-cocaine (Fig. 1). Regional analysis of radioactivity in the heart showed similar uptake in left ventricle and atrium. The peak ^{11}C concentrations for the left ventricle, septum and atrium were 0.007 (s.d., 0.001), 0.006 (s.d., 0.002), and 0.007 (s.d., 0.001) percent dose/cc, respectively. The uptake of ^{11}C in the heart reached a maximum value 2–3 min after administration of the tracer. Cardiac clearance was also fast, with half-peak activity seen 10 min after injection. In contrast to the heart, there was no retention of radioactivity by the lung, where activity was attributed to tracer in the plasma. Figure 2 shows the kinetics of ^{11}C uptake into the heart, lungs, and arterial plasma for one representative subject.

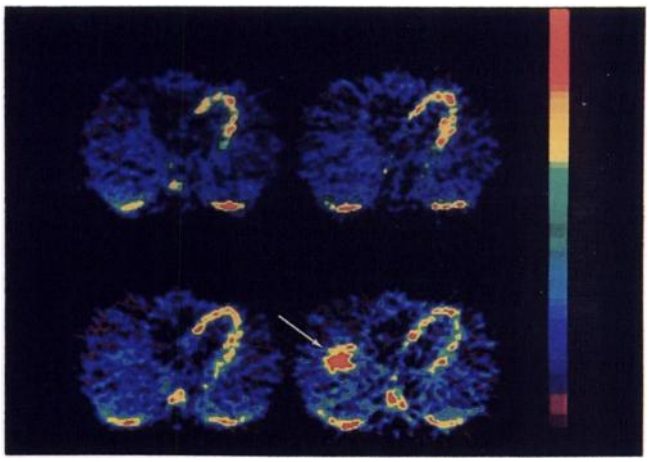

FIGURE 1. Thoracic images of ^{11}C-cocaine taken 2–10 min after injection. The images correspond to four contiguous axial planes showing the long-axis views of the heart. In the image on the lower right, one can visualize the upper portion of the liver (arrow). The images are scaled to the highest level of activity across all the slices.

Serial PET studies in one subject to assess differences over a 3-hr time interval between injections showed that the rate of uptake and kinetics of ^{11}C-cocaine were stable and reproducible. The variation was less than 5% for the uptake of ^{11}C-cocaine into the heart and liver, and the

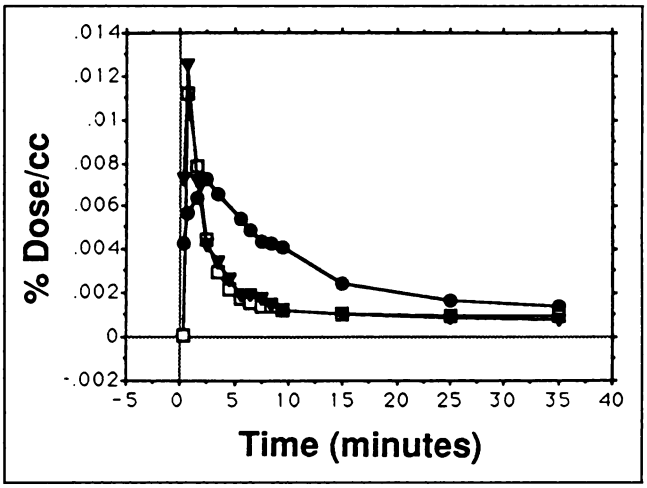

FIGURE 2. Time-activity curves of ^{11}C-cocaine in lung (□), heart (●), and plasma (▽) for a normal control. Uptake in the lung paralleled the radioactivity of plasma. In the heart, peak uptake occurred 2–3 min after injection. Half of the peak activity remained at 10 min.

time-activity curves for both studies were almost identical. Preadministration of benztropine mesylate did not affect the absolute uptake of ^{11}C-cocaine into the heart, nor did it change ^{11}C-cocaine kinetics in any of the four subjects studied.

The uptake of ^{11}C into the kidneys was limited mainly to the cortex (Fig. 3) and the time course was similar to that of the heart, with a maximum value at 2–3 min (0.014 (s.d., 0.002) percent dose/cc) and clearance to half of the maximum value at 10 min. In contrast to the fast uptake of ^{11}C into the heart and kidneys, cocaine and its labeled metabolites accumulated slowly in the liver, where their peak uptake was observed at 10–15 min (0.014 (s.d., 0.002) percent dose/cc) with a plateau for the rest of the scan (40 min).

Of the organs examined, the adrenals showed the highest uptake of ^{11}C with a peak corresponding to 0.032 (s.d., 0.001) percent dose/cc of tissue. Figure 3 shows the adrenals, kidney and liver images obtained with ^{11}C-cocaine in one of the subjects. Note the high uptake of ^{11}C-cocaine in the adrenals. Peak uptake in the adrenals occurred 10 min after injection and clearance to half peak value occurred at 22 min. The kinetics of ^{11}C-cocaine in adrenals are shown in Figure 4 with the kinetics of ^{11}C-cocaine in heart, lungs and liver shown for comparison.

Plasma analyses revealed that the amount of unchanged labeled cocaine in plasma was 98% (s.d., 2) at 1 min, 86% (s.d., 5) at 5 min, 75% (s.d., 7) at 10 min and 41% (s.d., 6) at 30 min.

DISCUSSION

This study documents significant uptake of ^{11}C by the human heart after the intravenous injection of ^{11}C-cocaine.

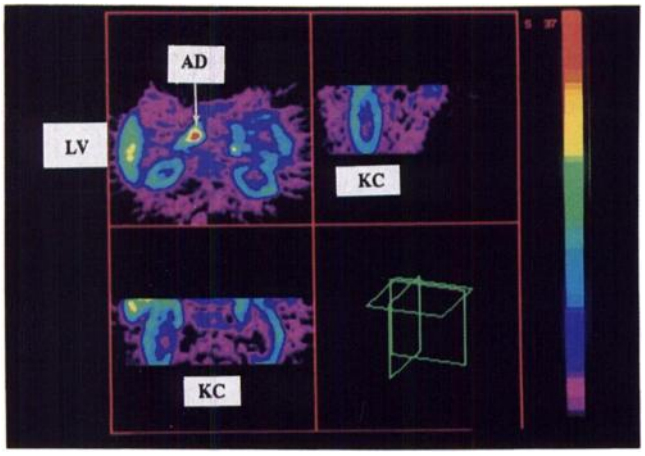

FIGURE 3. Images taken in the lower thorax with ^{11}C-cocaine 2–10 min after injection. The upper left corresponds to an axial plane, the upper right to a saggital plane and the lower left to a coronal plane. The diagram on the lower right shows the relationship of the different planes with one another. The images are normalized to the highest level of activity across all the planes. Notice the extremely high accumulation of cocaine into the adrenals (AD) as well as the accumulation of cocaine into the cortex of the kidneys (KC) and into the liver (LV).

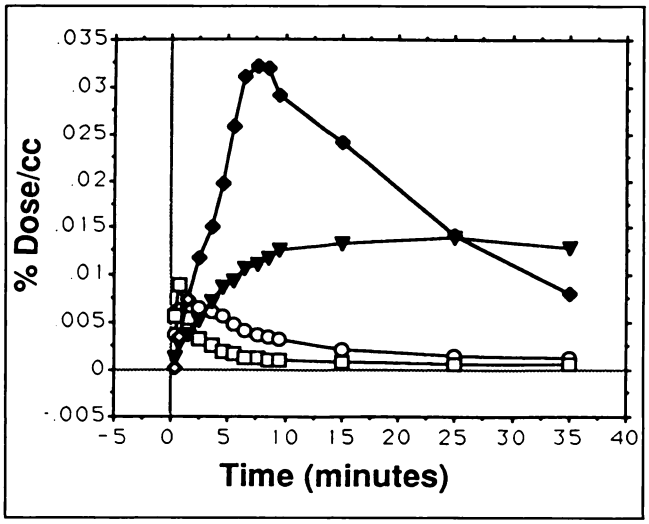

FIGURE 4. Average time-activity curves of ^{11}C-cocaine in the lung (□), heart (○), liver (▼), and adrenals (◆). Values represent the averages for 10 subjects, except for the adrenals which represent the averages for 2 subjects. Notice the differences among the rates of uptake and kinetics of ^{11}C-cocaine in various organs and the extremely high uptake of ^{11}C-cocaine in the adrenals.

For a heart weighing 350 g, 2.5% of the injected dose was in the heart 2–3 min after intravenous administration. The uptake and clearance of ^{11}C from the heart were faster than that for clearance from the brain (*20*). Cardiac clearance time to 50% of the maximum uptake was 10 min, whereas in the brain it was 25 min (*20*). The 2–3 min postinjection peak corresponds to the time required to reach maximal chronotropic response after intravenous injection of cocaine (*24*). However, the kinetics of cocaine clearance from the heart do not correspond to the longer lasting chronotropic effects of cocaine (*25*), which suggests that the prolonged chronotropic actions of cocaine are indirect. Indirect chronotropic effects on the heart could be due to central effects and/or to catecholamine release from the adrenals. The relatively long lasting chronotropic response to cocaine that persists when plasma levels of cocaine are negligible could be explained by sustained elevated plasma levels of epinephrine released from the adrenals by cocaine (*26*).

That there is significant accumulation of cocaine in the human heart suggests that cocaine could affect myocardial tissue directly via its interaction with noradrenergic transporters in myocardial cells (*27*) or via its local anesthetic properties at this site (*28*). Both of these properties may act synergistically to enhance cocaine's toxic effects. Although the cardiac accumulation of cocaine is transient after a single administration, under conditions of repeated administration (as used by the cocaine abuser), one would expect high concentrations throughout the period of drug administration.

Pretreatment with benztropine (an anticholinergic drug that also inhibits the dopamine transporter) did not affect

the binding of ^{11}C-cocaine to the heart. This is surprising since cocaine has been shown to bind to low-affinity (Ki 18.8 μM) muscarinic-cholinergic receptors in the human heart (*18*). However, cocaine binding to the muscarinic receptors in the heart may be below the level of detection of the PET camera. In future studies, pretreatment with specific norepinephrine transporter blockers and with cocaine may allow us to characterize the specificity of the binding of cocaine to the heart.

The uptake of ^{11}C-cocaine by the kidney was higher than for the heart and was limited to the cortex. The kinetics of ^{11}C-cocaine in the kidney were similar to those in the heart, suggesting that cocaine recognition sites in these two organs are similar and may correspond to the norepinephrine transporter. The cortex in the kidneys receives adrenergic innervation from postganglionic sympathetic nerve terminals. The effects of cocaine on adrenergic activity in the kidney could lead to changes in the renin angiotensin system since adrenergic innervation is one of the mechanisms that regulates renin release by the kidney (*24*). In fact, disruption by cocaine of the renin-angiotensin system has previously been reported (*29–31*) and could further contribute to the peripheral cardiovascular effects of cocaine (*32*).

There was no accumulation of cocaine in the lungs since the pulmonary kinetics of cocaine paralleled those of cocaine in the plasma. Even though norepinephrine uptake in the lungs have been demonstrated, the uptake process is extraneuronal and differs pharmacologically from that seen in neurons (*33*). The lack of observed binding of cocaine in the lungs could reflect a low density or absence of pulmonary binding sites for cocaine.

The hepatic accumulation of radioactivity after ^{11}C-cocaine is very high. Assuming an average liver weight of 1400–1600 g, the peak uptake of radioactivity in this organ corresponds to 20%–22% of the total injected dose. This uptake presumably represents cocaine and its metabolites (*34*). Cocaine uptake in the liver could reflect binding to a high affinity receptor site (Kd = 1.7 nmol) since pretreatment with 1 μmol cocaine has been shown to block its uptake (*35*). High cocaine uptake into the liver is of interest with respect to the hepatotoxicity of cocaine (*36*). At particular risk are subjects with pseudocholinesterase deficiencies for whom the main pathway for cocaine metabolism would be via the oxidative route (*34*). Because fetuses, infants, and pregnant women have low plasma cholinesterase activity, babies born to cocaine-abusing mothers are at particular risk for hepatotoxic complications (*37*).

The high levels of cocaine in the liver are in agreement with postmortem studies that showed concentrations of cocaine up to 20-fold higher in liver than in blood (*19*), as well as studies on liver membrane preparations reporting very high concentrations of cocaine-binding sites (*35*). The discrepancies reported by different investigators between plasma and liver concentrations in postmortem samples of cocaine abusers could be accounted for by the regional kinetics of cocaine, which show rapid disappearance from blood but slow accumulation and clearance from the liver. The difference in cocaine kinetics in vivo among various organs could explain the wide variability in postmortem concentrations of cocaine in these organs. If death immediately follows cocaine administration, a high concentration of cocaine could be expected in the lungs and plasma, whereas if death occurred at longer time intervals after cocaine administration, higher concentrations could be expected in the liver. Additionally, the nonenzymatic hydrolysis of cocaine (*38*) may also contribute variability in cocaine concentration when postmortem samples are analyzed at different time intervals after death.

The adrenals had the highest uptake of ^{11}C-cocaine and its kinetics were similar to those in the brain. Adrenal uptake probably represents binding to noradrenergic transporters since cocaine prevents uptake of noradrenaline in chromaffin cells (*39,40*). Catecholamines are released from adrenals by cocaine (*41,42*), perhaps via a CNS-mediated mechanism and via direct interaction with chromaffin cells (*10*). The patterns of ^{11}C-cocaine uptake by various organs of the human body are similar to those previously reported in rats using whole-body autoradiography and ^{14}C-cocaine (*43*).

CONCLUSION

The distribution and kinetics of ^{11}C in the heart, lungs, liver, kidneys and adrenals in normal human volunteers were studied after injection of [N-^{11}C methyl]cocaine. The highest uptakes were in the adrenals, liver, kidneys and heart. There was no pulmonary uptake. Although we have not determined whether the uptake in these organs represents labeled cocaine and/or labeled metabolites, the rapid uptake and clearance in heart and adrenals and the predominance of cocaine among labeled metabolites in plasma soon after injection argue for the image being predominantly labeled cocaine in hearts, kidneys, and adrenals, and predominantly cocaine and labeled metabolites in the liver, particularly at later times. Although we have demonstrated a finite and measurable residence time for cocaine in the heart, kidneys and adrenals, which is significantly longer than that in plasma, these initial studies do not allow us to determine whether this uptake represents binding to a specific receptor or re-uptake sites in the tissue, or whether they represent nonspecific accumulation of cocaine and/or its metabolite. Thus, the extent to which the accumulation of cocaine in these organs represents specific binding should be further investigated.

Cocaine is a potent local anesthetic and if it accumulates in the heart at a sufficient concentration it could interfere with membrane conductance. That cocaine accumulates to a considerable extent in the human heart supports the concept of direct interaction of cocaine with myocardial cells playing a role in the cardiotoxicity of cocaine. In addition, our observation of high cocaine uptake in the

adrenals suggests that the direct interaction of cocaine with chromaffin cells may be responsible for catecholamine release resulting in cardiac adrenergic stimulation.

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