Longer Occupancy of Opioid Receptors by Nalmefene Compared to Naloxone as Measured In Vivo by a Dual-Detector System

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Surgical procedures usually involve the administration of narcotic drugs as anesthetics or adjuvants. To reverse the effects of anesthesia, opioid antagonists such as naloxone are commonly used. Due to its short lasting effects, patients receiving naloxone must be monitored carefully. Nalmefene, a pure opiate antagonist with a longer duration of action than naloxone, has shown promise in the reversal of opioid anesthesia. **Methods:** A simple dual-detector positron radiation detection system and [11C]carfentanil were used to compare the duration of blockade of cerebral mu opioid receptors by naloxone and nalmefene in eight normal volunteers. Carbon-11-carfentanil brain kinetics were monitored for 5 min and 2, 4, 8 and 24 hr after the administration of either naloxone (1 mg or 1 μg/kg) or nalmefene (2 mg or 2 μg/kg). Blood samples were obtained at the same times for plasma determinations. **Results:** Clearance half-times from opioid receptors were 28.7 ± 5.9 hr for 1 mg of nalmefene and 2.0 ± 1.6 hr for 2 mg of naloxone. Brain clearance times were about 21.1 and 3.4 times slower than plasma clearance times for nalmefene and naloxone, respectively. **Conclusion:** These findings suggest that the prolonged effects of nalmefene are related to the slow dissociation of nalmefene from opioid receptors, which are not reflected in the plasma curve. This longer blockade of opioid receptors by nalmefene represents an advantage in the clinical management of postsurgical reversal of narcotic anesthesia and opioid side effects as well as the reversal of opioid overdose.

**Key Words:** positron emission; carfentanil; naloxone; nalmefene; dual-detector probe

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The central effects of opioids are mediated by multiple opiate receptor subtypes (1). The mu opiate subtype is highly concentrated in the thalamus and has been associated with analgesia and respiratory depression. The delta subtype is localized in the basal ganglia and may be involved in reward behavior and seizures, whereas kappa receptors are most highly concentrated in the cerebral cortex and amygdala and may be responsible for sedation. Surgical procedures usually involve the administration of narcotic drugs as anesthetics or adjuvants (2). Opioid antagonists are commonly used to reverse the effects of anesthesia (3) or to reverse the effects of a narcotic overdose. To date, intravenous administration of the opioid antagonist naloxone has been used at the end of surgery for postanesthesia reversal. Because the effects of the most commonly used anesthetics outlast those of naloxone, repeated administration or continuous infusion of naloxone often becomes necessary (4,5). Due to its limited duration of action, patients receiving naloxone must be monitored carefully in the recovery phase to prevent respiratory depression caused by anesthesia. On the other hand, administration of very large doses of naloxone can create too sudden a reversal of the narcotic effect, causing exacerbation of postsurgical pain or onset of withdrawal symptoms in persons who are physically dependent on narcotics (6,7).

Nalmefene (8,9), a pure opiate antagonist, has shown promise in the reversal of opioid anesthesia (10,11), with a longer duration of action than naloxone (12-14). Because opioid antagonists are not indicated after a procedure in which moderate or severe postoperative pain is anticipated, the advantage of nalmefene resides in its dose-dependent duration of action, preventing respiratory depression due to renarcotization in those patients in whom pain is effectively controlled by oral analgesics such as ibuprofen (because it outlasts the duration of action of commonly used narcotics) and also reducing prolonged observation times of patients who have received narcotics for their procedures (10).

Carfentanil is a potent, high-affinity synthetic opiate agonist that is 90 and 250 times more selective for mu than for delta and kappa opiate receptors subtypes, respectively (15). Carbon-11-carfentanil has been successfully used in PET studies to evaluate opiate receptors in humans in vivo (15,16). Carbon-11-carfentanil and a simple dual-detector system (17) have been proven to be useful in the determination of duration of opioid receptor occupancy by naltrexone (18) and in the in vivo characterization of different receptor ligands (19).

The purpose of this study was to compare the duration of opiate receptor occupancy by nalmefene and naloxone in a randomized, cross-over study, using a simple dual-detector system and [11C]carfentanil, and to relate the duration of opiate receptor occupancy to the plasma half-life of each opiate antagonist.

**MATERIALS AND METHODS**

Eight healthy volunteers (four men, four women; age range 18-65 yr; mean age 30.3 ± 15.5 yr) were recruited through local newspaper advertisements and paid for their participation. The study presented here was approved by the Institutional Review Boards of the Johns Hopkins Medical Institutions. All subjects gave written informed consent. The subjects were deemed healthy after a complete physical examination, including electrocardiogram and blood and urine assays. The subjects were instructed to abstain from nicotine, caffeine, alcohol and medication 24 hr before the study and were asked to fast overnight. All eight volunteers were randomly assigned to receive an intravenous administration of either 2 mg of naloxone and 1 mg of nalmefene (high doses) or 2
μg/kg naloxone and 1 μg/kg nalmefone (low doses) (Table 1). A ninth subject, a 22-yr-old man, received 2 mg of naloxone and 1 mg of nalmefone before [11C]carfentanil PET studies.

Data acquisition was performed using a simple dual-detector probe system that detects positron annihilation by coincidence detection of 511-keV gamma-ray pairs (17). The high sensitivity of the probe system allows quantification of changes in receptor occupancy studies to be performed with 1/50 of the dose required for a PET study, thus permitting the repetition of studies in the same subject (17). The subject’s head was positioned between the detectors so that the field of view (5 cm in diameter) would include the thalamus, caudate nucleus, putamen and overlying cerebral cortex (Fig. 1) using bone landmarks and a stereotactic frame. Each subject was fitted with a molded thermoplastic face mask that served as a head-stabilization device and alignment guide. Marks were drawn on the mask in the center of the field of view to ensure reproducibility of alignment between studies.

Carbon-11-carfentanil was synthesized according to published methods (20). All preparations were sterile and apyrogenic.

On the first study day, subjects were injected with 400–800 μCi of high-specific activity [11C]carfentanil (specific activity, >1000 Ci/mmol; injected mass of carfentanil ranging from 0.1 to 0.6 μg per injection). Time–activity curves were generated for 60 min after radiotracer injection. This baseline study was used to estimate total binding of [11C]carfentanil. After the [11C]carfentanil baseline study was obtained, total blockade of the subject’s opioid receptors was achieved by: an intravenous dose of 0.4 mg/kg naloxone 30 min before a second radiotracer injection; an additional 10 mg of naloxone 5 min before the radiotracer; and a continuous infusion of 21 μg/kg/hr naloxone that was started immediately after the injection of [11C]carfentanil. This dosage regimen of naloxone is known to block more than 90% of the available opioid receptors in the human brain (21). This study was used to estimate nonspecific binding.

During the 2 subsequent study days, each subject received a bolus intravenous injection of either naloxone or nalmefone at one of the two dose levels (see Table 1). Carbon-11-carfentanil was injected at 5 min, 2, 4, 8 and/or 24 hr after the administration of the naloxone or nalmefone, and time–activity curves were generated as previously described. After a 1-wk washout period, each subject returned for study with the opposing drug, at the corresponding dosage level, and data were acquired after the same procedures. Heart rate and blood pressure were monitored during each study.

Data were corrected for system dead time, random coincidences and radioactive decay. Activity was normalized to injected dose and body weight. Between 40 and 60 min after [11C]carfentanil injection, the radiotracer reaches equilibrium (21); therefore, all normalized activity values obtained between 40 and 60 min were averaged for subsequent analysis. The criteria used to estimate receptor occupancy included percent specific blockade of mu opioid receptors, clearance half-time (representing the disappearance of the blockade) and the washout rate of [11C]carfentanil. The percent specific blockade was obtained using Equation 1:

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Dose</th>
<th>Baseline</th>
<th>Total blockade</th>
<th>Time post-drug injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>66</td>
<td>H</td>
<td>+</td>
<td>+</td>
<td>5 min</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>37</td>
<td>H</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>21</td>
<td>L</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>28</td>
<td>L</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>22</td>
<td>H</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>25</td>
<td>L</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>19</td>
<td>L</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>24</td>
<td>H</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>22</td>
<td>H</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*PET study only.

H = high dose: Nalmefone, 1 mg, and naloxone, 2 mg; L = low dose: Nalmefone, 1 μg/kg, and naloxone, 2 μg/kg; + = studies done; − = studies not done; Nalox = study with naloxone only; Nalm = study with nalmefone only.

FIGURE 1. The dual-probe system used for detecting coincident 511-keV annihilation gamma rays. NaI = sodium iodide crystals; PMT = photomultiplier tube.
Percent specific blockade = \( \frac{TB - PB}{TB - NS} \times 100\% \), Eq. 1

where TB is total binding, the averaged activity between 40 and 60 min in the control study; PB is partial blockade, the averaged activity between 40 and 60 min in the studies 5 min, 2, 8 or 24 hr post-intravenous administration of either naloxone or nalmefene; and NS is the nonspecific binding, the averaged activity between 40 and 60 min in the total blockade study. The percent specific blockade for each time point for each drug dosage was averaged for the four subjects.

The clearance half-time of blockade was determined by fitting the percent blockade values at the different time points after naloxone or nalmefene administration to a monoexponential function. The washout of \(^{11}C\)-carfentanil from the brain was estimated from the slope of the normalized time–activity curve obtained between 5 and 15 min for each study. The slope, determined by linear regression, gives an indication of how rapidly unbound radiotracer leaves the brain, which is inversely proportional to the percentage of available receptors (\( \phi \)). Data were compared using paired, two-tailed Student’s t-tests. The criterion for significance was \( p < 0.05 \). No corrections for multiple comparisons were made.

Blood samples to measure plasma concentration of nalmefene and naloxone were collected before each radiotracer injection. Naloxone and nalmefene plasma concentrations were measured using specific radioimmunoassay methods (22,23). The plasma clearance half-lives for each drug was determined by fitting the plasma concentrations at the different time points to a double exponential function: \( C = Ae^{-\alpha t} + Be^{-\beta t} \), where \( C \) is the plasma concentration and \( \alpha \) and \( \beta \) are coefficients for the initial rapid distribution (\( \alpha \)) and elimination (\( \beta \)) phases, respectively. Plasma data were compared using paired, two-tailed Student’s t-tests. The criterion for significance was \( p < 0.05 \). No corrections for multiple comparisons were made. The relationship between receptor occupancy and plasma concentrations was analyzed using a Pearson correlation.

The duration of the effect of morphine and heroin ranges between 3 and 5 hr (6). To illustrate the difference in opioid receptor occupancy at a point in time in which an opioid abuser might be most vulnerable to seek renarcotization, two PET scans were performed on a ninth subject 8 hr after the administration of nalmefene and naloxone, respectively. Seven hours after receiving 2 mg of naloxone, the subject was positioned in the PET scanner, and a transmission scan was performed to allow for attenuation correction. Eight hours after receiving 2 mg of naloxone, the subject was injected with 18 mCi of \(^{11}C\)-carfentanil. PET scanning began immediately after \(^{11}C\)-carfentanil injection. Scanning continued for 90 min using the GE 4096+ PET tomograph in the high-resolution mode (~6.5 mm FWHM). Fifteen simultaneous slices were acquired (8 direct planes and 7 cross-planes). The lowest plane was ~35 mm below the canto-meatal line. PET images were reconstructed from the raw data with a standard filtered backprojection algorithm and a high-resolution Shepp–Logan filter. A week later, the subject underwent the same study 8 hr after receiving 1 mg of nalmefene.

RESULTS

Naloxone and nalmefene were well tolerated in all subjects. One subject reported light-headedness after the injection of 1 mg of nalmefene. No changes in blood pressure or heart rates were observed in any of the subjects.

Receptor occupancy by nalmefene lasted significantly longer than receptor occupancy by naloxone. Normalized time–activity curves indicated that the 8-hr postnaloxone curve was not significantly different (\( p > 0.05 \)) from the total blockade curve (Fig. 2). Normalized time–activity curves 8 hr postnaloxone were not significantly different (\( p > 0.05 \)) from the control curve (Fig. 3). The clearance half-time of the blockade was 28.6 ± 5.9 hr for nalmefene and 2.0 ± 1.6 hr for naloxone (Fig. 4).

The percent specific blockades by nalmefene and naloxone at high- and low-dose treatment regimens are presented in Table 2. At 5 min, the degree of receptor occupancy by 1 mg of nalmefene was higher than that for 2 mg of naloxone, although the increase was not statistically significant. At 2, 4 and 8 hr after the administration of the opioid antagonists, 1 mg of nalmefene showed a significantly (\( p > 0.05 \)) higher degree of receptor occupancy than did 2 mg of naloxone. The same pattern was observed for the low-dose treatment regimens.
although the degree of receptor occupancy was much lower for both opioid antagonists (Table 2), and the differences between them were not significant.

The washout rate of $[^{11}]$ C] carfentanil from the brain, as measured by the slope index, was faster for nalmefene than that for naloxone (Table 3). The lower dose treatments did not show a noticeable difference in the slopes.

The clearance of 1 mg of nalmefene from plasma had a half-time of 1.36 ± 0.17 hr, compared to 0.59 ± 0.28 hr for 2 mg of naloxone (Table 4). Pearson correlation coefficients between plasma values and percent specific blockade were 0.31 for nalmefene and 0.04 for naloxone.

The summed 40–60-min PET images from each study (Fig. 5) illustrate the difference between the degree of occupancy of opioid receptors 8 hr after the administration of nalmefene and naloxone. The PET images are in agreement with the results obtained with the dual-probe system, showing greater receptor occupancy by nalmefene than naloxone.

DISCUSSION

A rational approach to developing dosage regimes or to designing and monitoring drug treatments in human subjects can be achieved by obtaining kinetic information over the specific site of pharmacological action rather than relying on

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**FIGURE 3.** Time-activity curves at 5 min (○) and 2 (△), 4 (△) and 8 (○) hr after the administration of 2 mg of naloxone.

**FIGURE 4.** Comparison of the clearance half-time of the percent blockade for each of the two antagonists. Nalmefene (●) showed a longer clearance half-life than naloxone (△).
blood levels of the drug. The dual-detection system is of particular value in assessing stereoselective binding of drugs to receptors in vivo and helps elucidate the pharmacokinetics (18) and dose–response characteristics of various opiate receptor ligands (19) in the human brain. With the dual-detection system, it is possible to determine the minimum dose of a drug required to block or occupy a certain receptor site, avoiding higher than needed doses and reducing side effects. Furthermore, valuable data is obtained with very low radiation exposure to the subject (17). The use of specific radiotracers in combination with the dual-detection system has allowed us to examine the pharmacokinetics of nalmefene and naloxone in human subjects.

Our results indicate that nalmefene blocked mu opioid receptors for a significantly longer period of time than naloxone. This persistence of occupancy by nalmefene was also manifested by a faster clearance of the unbound [11C]carfentanil from the brain. In contrast, naloxone-treated subjects, having greater receptor availability, showed a slower clearance of the radiotracer from the brain. Both drugs block the opioid receptors in the brain for a longer period than might be suggested by the plasma values. The discrepancy between the clinical effect of nalmefene (13,14,24) and its plasma t1/2 can be explained by the persistent binding of nalmefene to the receptors, as suggested by a higher in vitro affinity for the central mu receptor subtype (IC50 values of 1.0 nM and 4.0 nM for nalmefene and naloxone, respectively) (25).

One milligram of nalmefene was shown to be a longer-lasting opioid antagonist than was 2 mg of naloxone when given intravenously. Our results indicate that nalmefene might offer a clinical advantage to prevent complications, such as respiratory depression, from narcotic anesthesia for a longer period of time. Our results also indicate that nalmefene might prove to be a better opiate antagonist in the management of the reversal of opioid overdose.

### CONCLUSION

The dual-detector system is a suitable tool for the evaluation of the pharmacokinetic characteristics of drugs at the specific site of pharmacological action. These findings suggest that the prolonged effects of nalmefene are related to the slow dissociation of nalmefene from opioid receptors, which are not reflected in the plasma curve. This longer blockade of opioid receptors by nalmefene might represent an advantage in the clinical management of the reversal of narcotic anesthesia and of opioid overdose.

### TABLE 2

#### Percent Specific Blockade

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5 min</th>
<th>2 hr</th>
<th>4 hr</th>
<th>8 hr</th>
<th>24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxone, 2 mg</td>
<td>80.6 ± 2.6</td>
<td>47.2 ± 4.0</td>
<td>43.8 ± 7.3</td>
<td>7.1 ± 5.4</td>
<td>N/A</td>
</tr>
<tr>
<td>Nalmefene, 1 mg</td>
<td>99.5 ± 7.8</td>
<td>90.3 ± 4.7*</td>
<td>96.0 ± 2.0*</td>
<td>85.7 ± 7.6*</td>
<td>53.3 ± 10.0</td>
</tr>
<tr>
<td>Naloxone, 2 μg/kg</td>
<td>42.6 ± 8.9</td>
<td>6.2 ± 6.3</td>
<td>33.1 ± 10.0</td>
<td>10.0 ± 11.4</td>
<td>N/A</td>
</tr>
<tr>
<td>Nalmefene, 1 μg/kg</td>
<td>52.2 ± 12.4</td>
<td>33.1 ± 21.2</td>
<td>47.5 ± 3.5</td>
<td>26.5 ± 16.0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Statistically significant by Student's t-test, p < 0.05.

Each value is the mean ± s.e.m. for 3 or 4 subjects. The percent specific blockade was obtained using Equation 1 (see text). N/A = not applicable.

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### TABLE 3

#### Slope Index for Carbon-11-Carftentanil

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5 min</th>
<th>2 hr</th>
<th>4 hr</th>
<th>8 hr</th>
<th>24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxone, 2 mg</td>
<td>-0.26 ± 0.03</td>
<td>-0.16 ± 0.03</td>
<td>-0.09 ± 0.00</td>
<td>-0.02 ± 0.04</td>
<td>N/A</td>
</tr>
<tr>
<td>Nalmefene, 1 mg</td>
<td>-0.29 ± 0.02</td>
<td>-0.23 ± 0.02</td>
<td>-0.20 ± 0.00*</td>
<td>-0.20 ± 0.02*</td>
<td>-0.15 ± 0.02</td>
</tr>
<tr>
<td>Naloxene, 2 μg/kg</td>
<td>-0.17 ± 0.04</td>
<td>-0.09 ± 0.02</td>
<td>-0.07 ± 0.02</td>
<td>-0.06 ± 0.04</td>
<td>N/A</td>
</tr>
<tr>
<td>Nalmefene, 1 μg/kg</td>
<td>-0.23 ± 0.10</td>
<td>-0.11 ± 0.04</td>
<td>-0.08 ± 0.02</td>
<td>-0.07 ± 0.03</td>
<td>-0.05 ± 0.00</td>
</tr>
</tbody>
</table>

*Statistically significant by Student's t-test, p < 0.05.

Each value is the mean ± s.e.m. for 3 or 4 subjects. The washout rate was estimated by linear regression from the slope of the normalized time–activity curve between 5 and 15 min. N/A = not applicable.

### TABLE 4

#### Plasma Levels

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5 min</th>
<th>2 hr</th>
<th>4 hr</th>
<th>8 hr</th>
<th>Distribution</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxone, 2 mg</td>
<td>38.71 ± 21.59</td>
<td>1.85 ± 0.24</td>
<td>0.69 ± 0.16</td>
<td>0.16 ± 0.03</td>
<td>0.33 ± 0.14</td>
<td>1.31 ± 0.17</td>
</tr>
<tr>
<td>Nalmefene, 1 mg</td>
<td>13.56 ± 7.21</td>
<td>4.82 ± 2.95</td>
<td>1.35 ± 0.24</td>
<td>0.64 ± 0.06</td>
<td>1.15 ± 0.29*</td>
<td>8.30 ± 0.34*</td>
</tr>
<tr>
<td>Naloxene, 2 μg/kg</td>
<td>2.26 ± 1.72</td>
<td>0.39 ± 0.32</td>
<td>0.08 ± 0.01</td>
<td>0.07 ± 0.00</td>
<td>0.33 ± 0.23</td>
<td>1.91 ± 0.27</td>
</tr>
<tr>
<td>Nalmefene, 1 μg/kg</td>
<td>16.64 ± 16.39</td>
<td>0.10 ± 0.01</td>
<td>0.09 ± 0.02</td>
<td>0.06 ± 0.01</td>
<td>0.32 ± 0.14</td>
<td>10.9 ± 0.25*</td>
</tr>
</tbody>
</table>

*Statistically significant by Student's t-test, p < 0.05.

†Great variance was observed in the plasma levels for the low dose of nalmefene. The blood levels were at the limits of sensitivity of the assay technique (23).

Each value is the mean ± s.e.m. for 3 or 4 subjects. Units are ng/ml. The plasma clearance t1/2 were estimated by double exponential fit of the plasma values.
Figure 5. PET scans obtained 8 hr after the administration of 2 mg of naloxone (left) and 1 mg of nalmefene (right). The binding of \(^{11}\text{C}\)-carfentanil in the striatum and thalamus after nalmefene administration is significantly less than that after naloxone administration.

Acknowledgments

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References


Metabolism of Technetium-99m-L,L-Ethyl Cysteinyl Dimer in Rat and Cynomolgus Monkey Tissue

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Technetium-99m-L,L-ethyl cysteinyl dimer (\(^{99}\text{m}\)Tc-ECD) is thought to be hydrolyzed in the brain by an enzyme and to be trapped as a hydrophilic product. We investigated the characteristics of the enzymatic system that metabolizes \(^{99}\text{m}\)Tc-ECD. Methods: In 50 mM phosphate buffer (pH 7.4), \(^{99}\text{m}\)Tc-ECD was incubated with various concentrations of homogenates of rat tissues (blood, liver and brain) or cynomolgus monkey tissues (blood, liver, cerebral gray matter, cerebral white matter and cerebellar gray matter), and the metabolic rates were assessed. Inhibition studies were performed using disopropyl fluorophosphate, eserine and p-chloromercuribenzoate as inhibitors. The metabolic rates in the brain homogenates of rat and monkey were measured at various levels of pH, ranging from 6.6 to 7.6. Technetium-99m-L,L-ethyl cysteinyl dimer metabolism was also examined in the presence of purified enzymes. Results: In both species, the metabolic rate was high in liver tissue, intermediate in brain tissue and low in blood. The rate in cerebral gray matter of cynomolgus monkey was higher than those in rat brain, monkey cerebral white matter and monkey cerebellar gray matter. All substances used as inhibitors depressed \(^{99}\text{m}\)Tc-ECD metabolism, and the response was different among tissues. Reduction in pH induced slight decreases in metabolic rate. Hydrophilic conversion of \(^{99}\text{m}\)Tc-ECD was observed after incubation with porcine liver carboxylesterase. Conclusion: These results support the hypothesis that the hydrophilic conversion of \(^{99}\text{m}\)Tc-ECD is mediated by enzymes. It is also suggested that various enzymes catalyze the hydrolysis of \(^{99}\text{m}\)Tc-ECD and that the enzymatic system that metabolizes \(^{99}\text{m}\)Tc-ECD is different between tissues and between species.

Key Words: technetium-99m-ECD; metabolism; in vitro

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Technetium-99m-L,L-ethyl cysteinyl dimer (\(^{99}\text{m}\)Tc-ECD), a brain perfusion agent for SPECT, is widely used in various clinical situations (1). After its intravenous injection, \(^{99}\text{m}\)Tc-