Comparison of Iodine-123-Epidepride and Iodine-123-IBZM for Dopamine D2 Receptor Imaging

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Although ^{123}I-IBZM is widely used as a D2 receptor imaging agent, image quality is compromised by a relatively low target-to-nontarget ratio. Animal studies suggest that ^{123}I-epidepride (K_d 0.024 n*M*) may be superior to ^{123}I-IBZM, but this agent has not been systematically studied in humans. **Methods:** We directly compared ^{123}I-epidepride and ^{123}I-IBZM in five normal volunteers (age range 30–58 yr, mean 43 yr). Brain SPECT imaging was performed 2 hr after the ^{123}I-IBZM injection (average dose 153 MBq). Iodine-123-epidepride scans were performed 1 hr (n = 3), 2 hr (n = 5) and 3 hr (n = 3) postinjection (average dose 149 MBq). **Results:** Both radiopharmaceuticals were well tolerated. Iodine-123-epidepride provided excellent visualization of the striatum. Percent specific striatum uptake at 2 hr (71.7 ± 4.9%) was much greater than with ^{123}I-IBZM (32.6 ± 5.3%, $p < 0.01$). **Conclusion:** Iodine-123-epidepride is a new D2 receptor agent that exhibits excellent neuroimaging properties and has a much higher affinity for striatal uptake than ^{123}I-IBZM.

Key Words: neuroimaging; neurotransmitter; dopamine

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Nuclear medicine is rapidly establishing itself as an important tool in the in vivo study of brain neurochemistry. In particular, several radioligands for the dopamine D2 receptor have been developed and these have offered valuable new insights into the role of dopamine in disorders of locomotor function, psychiatry and genetic disease (*1–5*). Fluorine-18-N-Methylspiroperidol (NMSP), a PET agent for studying the D2 receptor, has demonstrated high target-to-nontarget uptake in the striatum, but this is not the case with ^{123}I-IBZM (^{123}I-S-(-)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-3-iodo-6-methoxybenzamide), the most widely used SPECT radiopharmaceutical (*6*). As a result, investigators have been actively seeking SPECT radiopharmaceuticals for the D2 receptor with greater receptor affinity. Animal studies have suggested that epidepride might exhibit high levels of striatal-to-background uptake related to enhanced affinity for the D2 receptor (*7,8*), but the published human experience with this agent is limited to a single case report (*9*). Therefore, we undertook a direct comparison of ^{123}I-epidepride and ^{123}I-IBZM SPECT in normal control subjects.

MATERIALS AND METHODS

Subjects

Brain SPECT was performed twice in each of five normal volunteers (age range 30–58 yr, mean 43 yr), once with ^{123}I-IBZM and then again with ^{123}I-epidepride (interval between scan 1–10 wk). The study protocol was approved by the local ethics committee for human research. Subjects were recruited from relatives with a family history of Huntington's disease but, after complete neuropsychiatric assessment and direct DNA analysis, were considered to be at very low risk for the disorder. Subjects were selected from a larger study investigating the role of dopamine receptor imaging in individuals who are either clinically affected by Huntington's disease or who are predicted to be at high risk based upon DNA analysis. No subject was receiving medications known to interfere with dopamine metabolism or uptake. Potassium iodide 130 mg daily was administered for 5 days starting 24 hr before radiopharmaceutical injection. After insertion of an intravenous line the subject was allowed to sit quietly in a private room for 10 min under ambient light and noise conditions before radiopharmaceutical injection.

Radiopharmaceutical

Iodine-123-IBZM was prepared using a slight modification of a previously described procedure (*10*) by oxidative radioiodination of BZM (4 μg) (see Acknowledgments) using peracetic acid and ^{123}I-NaI at pH 4 (0.5 *M* ammonium acetate buffer). The reaction was quenched with sodium metabisulfite, neutralized with sodium bicarbonate, adsorbed onto a C18 Sep Pak and washed with normal saline (5 ml) to remove unreacted iodide. Iodine-123-IBZM was removed from the Sep Pak by retrograde elution with ethanol (95%) and diluted with normal saline for injection. Overall radiochemical recovery of ^{123}I-IBZM ranged from 33% to 62% of starting activity. Product radiochemical purity, determined by silica gel instant thin-layer chromatography (chloroform:methanol 9:1 v/v), ranged from 88% to 96%, with free ^{123}I-iodide identified as the major impurity.

Iodine-123-epidepride was prepared by iododestannylation of the tributyl-tin epidepride (5 μg) derivative (S-(-)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-tributylstannyl-2,3-dimethoxybenzamide) (see Acknowledgments) using hydrogen peroxide (5 μl of 3% v/v) in 4 N HCl (5 μl). The reaction was quenched by the addition of sodium metabisulfite (5 μl saturated solution) and neutralized with 4 N ammonium hydroxide (5 μl). The final reaction mixture was diluted by one-half with high-pressure liquid chromatography (HPLC) solvent (70/30 ethanol/phosphate buffer, v/v) and purified by HPLC (C18 reverse-phase, 0.5 ml/min, R_t = 12 min). Overall radiochemical recovery of ^{123}I-epidepride ranged from 77% to 94% of starting activity. Product radiochemical purity, determined by rp-HPLC (same as preparative conditions) and silica gel thin-layer chromatography (chloroform/methanol, 9:1, v/v), ranged from 92% to 99%, with free ^{123}I-iodide identified as the major impurity. All solvents and chemicals were purchased commercially and used without further purification unless otherwise specified.

Image Acquisition

Brain SPECT imaging was performed 2 hr after ^{123}I-IBZM injection (average dose 153 MBq), while the ^{123}I-epidepride scans were obtained 1 hr (n = 3), 2 hr (n = 5) and 3 hr (n = 3) postinjection (average dose 149 MBq). Scans were acquired with a dual-head gamma camera using high-resolution, low-energy, parallel-hole collimators. The camera had been fitted with a custom-built headholder which allowed for a minimal radius of rotation. Four point sources, each containing 0.1 MBq ^{123}I, were used to

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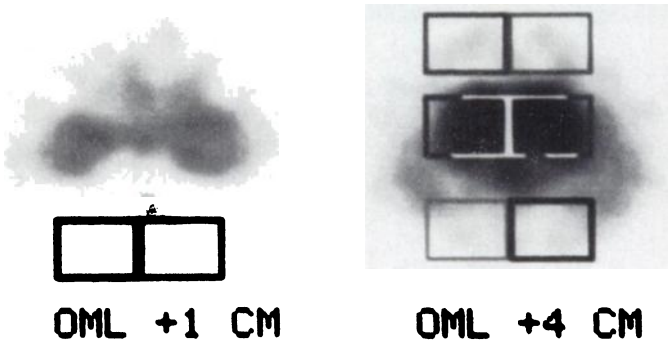

FIGURE 1. ROI placement for (A) cerebellum and (B) striatum, frontal cortex and occipital cortex.

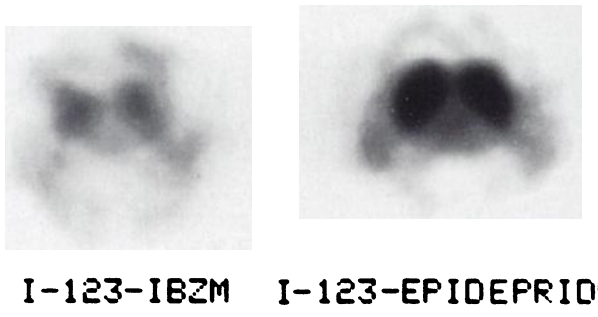

FIGURE 2. Two-hour postinjection ^{123}I-IBZM (left) and ^{123}I-epidepride (right) scans from a single subject. Striatum-to-frontal cortex ratios were 1.73 and 3.85, respectively.

define the orbitomeatal line (OML) and these were left in place throughout the period of data acquisition. Each detector acquired 120 projection images (15 sec per projection) over a 360° auto-contoured orbit. Data were collected into 128 × 128 unzoomed matrix format (0.22 cm pixel^{-1}). This imaging system has been shown to have a reconstructed FWHM of 9 mm in water at the center of a 15-cm radius of rotation.

Image Analysis

Data were reconstructed using filtered backprojection (Butterworth filter with order 5 and cutoff 0.35 cycles cm^{-1}) and postprocessing attenuation correction (0.09 cm^{-1}). The images were reoriented parallel to the OML using the external reference markers and adjacent slices were summed to give 2-cm thick composite slices centered on the striatum, cerebellum and external markers. Circular ROIs were centered over each of the external markers and a rectangular ROI (14.5 cm^2) was manually positioned over each striatal nucleus (OML+4 cm). The striatal ROIs were used to align a template defining equal-sized ROIs for the cerebellum (OML+1 cm), frontal cortex (OML+4 cm), and occipital cortex (OML+4 cm) (Fig. 1). Specific binding (striatal counts minus occipital counts) was calculated for the three subjects who underwent serial ^{123}I-epidepride scans. Percent specific striatal uptake was calculated from the striatum and occipital cortex according to the method of Seibyl et al. (*11*):

$$\frac{\text{Striatum} - \text{Occipital cortex}}{\text{Striatum}} \times 100\%$$

Statistical Analysis

All analyses were performed with CSS:Statistica v3.1 (StatSoft Inc., Tulsa OK). Results are expressed as mean ± s.d. Measures of striatal uptake were compared with the Mann-Whitney U-test, with $p < 0.05$ indicating statistical significance.

RESULTS

Both radiopharmaceuticals were well tolerated except for minor irritation from the ethanol vehicle during the ^{123}I-epidepride infusion. Visually, the ^{123}I-epidepride scans provided striatum visualization consistently superior to that of ^{123}I-IBZM (Fig. 2). There was consistent but faint extrastriatal uptake of ^{123}I-epidepride in the thalamus and temporal cortex, and this exceeded nonspecific background uptake in the frontal and occipital cortices.

Specific striatal binding of ^{123}I-epidepride, expressed relative to the 1hr scan, was relatively constant over the 3 hr of imaging (100% at 1 hr, 108% at 2 hr, 105% at 3 hr). Relative to the frontal cortex, striatal uptake was 2.51 ± 0.37 at 1 hr, 3.38 ± 0.65 at 2 hr and 4.96 ± 0.57 at 3 hr (Table 1). High ratios were also seen when striatal uptake was related to the occipital cortex or cerebellum. Again, these were consistently and significantly greater than those obtained with ^{123}I-IBZM. Percent specific striatal uptake with ^{123}I-epidepride was 59.4% ± 5.2% at 1 hr, 71.7% ± 4.9% at 2 hr and 79.8% ± 1.1% at 3 hr (Fig. 3). At each time, there was greater specific striatal uptake with ^{123}I-epidepride than the 32.6% ± 5.3% seen with ^{123}I-IBZM ($p < 0.05$ for all comparisons).

DISCUSSION

In vitro studies have demonstrated that ^{123}I-epidepride has a very high affinity for the dopamine D2 receptor (K_d 0.024 n*M*). Substantially lower affinities (indicated by greater values for K_d) have been reported with ^{123}I-IBZM (K_d 0.426 n*M*), ^{123}I-ILIS (0.27 n*M*) and ^{123}I-IBF (0.106 n*M*) (*12–14*). Only NC-298, an iodinated salicylamide, has comparable receptor binding properties, but experience with this new agent is still quite limited (*15*).

Our in vivo characterization of ^{123}I-epidepride is consistent with the in vitro data. Relative striatal uptake, expressed as a ratio of striatum-to-frontal cortex counts, was much greater than that observed with ^{123}I-IBZM (3.38 ± 0.65 versus 1.52 ± 0.19, $p < 0.01$). Our results with ^{123}I-IBZM are quite close to other published ranges for normal controls [1.74 ± 0.10 at 60 min (*2*), 1.58 ± 0.06 at 60 min (*16*), 1.55 ± 0.05 at 120 min (*3*)]. Although published human data on other agents are limited, ^{123}I-epidepride also appears to be superior to ^{123}I-ILIS [striatum-to-cerebellum, 1.52 ± 0.19 at 60 min (*13*)] and ^{123}I-IBF [striatum-to-frontal cortex, 2.48 ± 0.19 at 120 min (*17*)]. Considerable differences have also been reported with PET dopamine D2 receptor agents. Our results with ^{123}I-epidepride compare favorably with those observed using ^{76}Br-bromospiperone [striatum-to-cerebellum 1.8 at 4.5 hr (*18*)] and ^{18}F-NMSP [estimated striatum-to-frontal cortex 3.3 at 120 min (*6*)].

Varying densities of dopamine D2 receptors have been demonstrated throughout the human brain, but concentrations in

TABLE 1
Striatal Uptake of ^{123}I-Epidepride and ^{123}I-IBZM Relative to Frontal Cortex, Occipital Cortex and Cerebellum (mean ± s.d.)

Tracer	Striatum/ Frontal cortex	Striatum/ Occipital cortex	Striatum/ Cerebellum
Epidepride (1 hr)	2.51 ± 0.37*	2.49 ± 0.30*	2.75 ± 0.23*
Epidepride (2 hr)	3.38 ± 0.65†	3.60 ± 0.52†	4.22 ± 1.00†
Epidepride (3 hr)	4.96 ± 0.57*	4.97 ± 0.29*	6.41 ± 1.67*
IBZM (2 hr)	1.52 ± 0.19	1.49 ± 0.13	1.56 ± 0.17

* $p < 0.05$ compared with ^{123}I-IBZM.
† $p < 0.01$ compared with ^{123}I-IBZM.

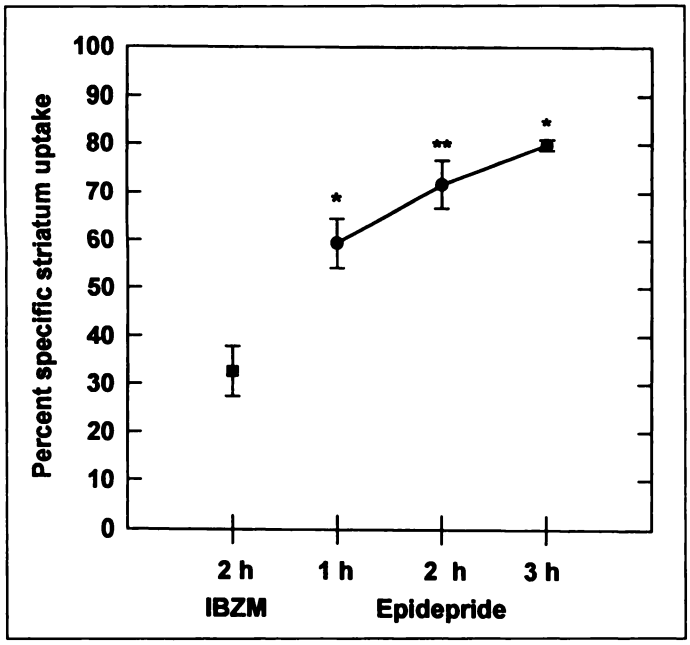

FIGURE 3. Percent specific striatum uptake for ^{123}I-epidepride compared with ^{123}I-IBZM (mean ± s.d.). * $p < 0.05$ compared with ^{123}I-IBZM, ** $p < 0.01$ compared with ^{123}I-IBZM.

the striatum (16.5 pmole/g tissue) are many times greater than those of the thalamus (0.72–1.0 pmole/g), hypothalamus (1.8 pmol/g), pituitary (1.3 pmole/g) and temporal cortex (0.31–0.46 pmole/g) (*19*). Our in vivo results are consistent with this distribution of receptors but, in contrast to the high affinity striatal accumulation of ^{123}I-epidepride, we found only low levels of specific uptake in the extrastriatal sites. Our failure to visualize receptor uptake in the hypothalamus and pituitary probably relates to the smaller volumes of these structures.

It is important to stress that a favorable target-to-background ratio is not sufficient to establish the imaging utility of a radiotracer. Factors related to the radiopharmaceutical itself (ease of preparation, radiopharmaceutical purity, availability and cost), ligand-receptor interaction (reversibility, specificity), in vivo localization (rate of blood clearance, blood-brain barrier permeability, ligand metabolism) and clinical application (characterizing receptor number, receptor affinity or endogenous displacement) also affect radiopharmaceutical choice (*8,20*).

In summary, ^{123}I-epidepride gives high-quality images of the striatum consistent with its known enhanced in vitro receptor affinity.

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EDITORIAL

SPECT Imaging of Dopamine Receptors

PET has become an established method for the in vivo study of neurotransmitter systems. It provides not only unique information of potential clinical significance in several important neuropsychiatric disorders, but it also allows investigation of drug actions in the living human brain. Imaging of some neurotransmitter systems, particularly the dopaminergic and benzodiazepine systems, has also become feasible using SPECT due to the recent development of iodinated neuroligands and advancements in SPECT technology. Both the widespread availability and the lower operating costs of SPECT compared with PET suggest that SPECT imaging of neurotransmitter systems may become an important clinical tool.

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