

AN INVESTIGATION ON RADIOPHARMACEUTICAL POTENTIAL OF I-131 LABELED SERTRALINE

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ABSTRACT

Sertraline [(1S- cis)- 4-(3, 4-dichlorophenyl)-1,2,3,4 -tetrahydro – N-methyl-1-naphalenamine hydrochloride] is an antidepressant drug. It is presumed to be linked to its inhibition of central nervous system (CNS) neuronal uptake of serotonin (5-HT) receptors. Serotonin 5-HT_{1A} receptors are prominently expressed in the CNS that binding sites are present various brain regions.

The aim of this study is to label with I-131 and investigate of its radiopharmaceutical potential. Sertraline was labeled with I-131 by using iodogen method. Quality Controls were fixed by Radio-TLC and Electrophoresis Methods. Labeling yield was 85-90% and specific activity was approximately 1.75 Ci/mmol. The purification of radioiodinated Sertraline was performed by Sep Pak C-18 plus and determined radiochemical purity over 99%. Biodistribution studies were carried out by male Albino Wistar rats. I-131 labeled Sertraline was administered by intravenous injection into tail vein of the rats. The rats were sacrificed by ether narcotization at certain time intervals and the organs were removed. The whole brain was excised quickly and dissected into their regions. Their activities were counted by Cd(Te) detector equipped with RAD 501 Single Channel Analyzer Instrument. The percentage injected radioactivity per gram of tissue was calculated, and these data versus time curves were generated for organs and brain regions.

Obtained results showed that I-131 labeled Sertraline may be a promising radiopharmaceutical for investigation of serotonin 5-HT receptor functions of brain.

INTRODUCTION

Sertraline hydrochloride, a central nervous system serotonin reuptake inhibitor, has been shown to be an effective treatment of hypotension caused by autonomic dysfunction in disorders such as neurocardiogenic syncope and idiopathic orthostatic hypotension. Sertraline is an antidepressant for oral administration (Figure 1) (1).

5-HT₁ like receptors include, according to the current knowledge, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D} receptors. All of them display nanomolar affinity for 5-HT. In contrast, 5-HT₂ receptors are apparently homogenous and only have micromolar affinity for 5-HT. The 5-HT₃ receptor

class has been reported to include three subtypes, although heterogeneity has not been confirmed by radioligand binding studies, successfully applied recently to the investigation of this class of 5-HT receptors (2, 3).

Welch et al. prepared 7-³H-Sertraline(4). In another investigation to imaging in brain 5-HT_{1A} receptors with positron emission tomography (PET), N-(2-(4-(2-Methoxy-phenyl)-1-piperazin-1-yl)ethyl)-N-(2-pyridyl)cyclohexanecarboxamide (WAY-100635) was labelled in its amido carbonyl group with ¹¹C ($t_{1/2}$ = 20.4 min) and PET experiments in six cynomolgus monkeys and seven healthy male volunteers, [Carbonyl-¹¹C]WAY-100635 was taken up avidly by brain (5, 6). Farde and coworkers examined that the prospects for quantitation of Carbonly-¹¹C-WAY 100635 binding to 5-HT_{1A} receptors in the human brain (6). Radioactivity was retained in regions rich in 5-HT_{1A} receptors, such as occipital cortex, temporal cortex and raphe nuclei, but cleared rapidly from cerebellum, a region almost devoid of 5-HT_{1A} receptors (5).

The aim of this study was to label Sertraline with I-131 and investigate of its radiopharmaceutical potential as a serotonin receptor agent.

MATERIAL AND METHODS

Sertraline was obtained from Center for Drug Research Development and Pharmacokinetic Applications. Na¹³¹I was provided from the Department of Nuclear Medicine. All other chemicals were purchased from Merck.

Radio-Thin Layer Chromatography was carried out by using cellulose-coated plastic sheets (Merck 5565). The plastic sheets with a thickness of 0.1mm were cut into 1x10 cm strips and used for quality control of radiopharmaceutical. The sample was applied marked point and developed in two different solvent systems which were n-butanol (pure) (solvent 1) and Isopropyl alcohol/n-butanol/0,2N ammonium hydroxide (solvent 2). The strips were dried and cut into 0.5 cm parts. The radioactivity of each part was counted by Cd(Te) detector equipped with RAD 501 Single Channel Analyzer Instrument. RTLC chromatograms were acquired from these counts.

Electrophoresis was fulfilled with a Gelman electrophoresis chamber supply using cellulose acetate strips (1cmx25 cm). Application point and others (anode and cathode poles) were marked on these strips and were moistened by buffer solution which was a mixture n-butanol/water/acetic acid. After sample was applied strips, they were set in the electrophoresis chamber.

Standing time and applied voltage were two hours and 300 Volt, respectively. Developed strips were dried and cut into 1 cm pieces. They were counted by Cd(Te) detector equipped with RAD 501 Single Channel Analyzer Instrument. Electrophoresis diagrams were obtained from these counts.

Labeling procedure:

One milligram Sertraline was dissolved in 5% ethanol solution. This solution was put in iodogen coated tube (2mg). Then 1-3 mCi (37-111 MBq) Na¹³¹I was added to reaction mixture. The solution was incubated for 20 minutes at room temperature. The reaction was ended by adding 0.1 N Na₂SO₃ solution (100 µL).

Radiochemical yield was determined by RTLC and paper electrophoresis methods. The resultant solution was transferred to a syringe attached to a CSP (C-18 Sep Pak) and passed through the CSP (7). Radiochemical purity was determined by same analyze methods again.

Biodistribution Study:

The protocol was approved by the Institution Animal Review Committee. Biodistribution study was performed using male Albino Wistar 4 rats (150-200 g). Ethanol-water solution of ¹³¹I-Sertraline was purified by CSP (C-18 Sep Pak). The resultant solution was diluted with saline solution (0.09%) (10 mL) and filtered by sterile-membrane filter (0,22 µm) into a sterile injection vial. The rats was administrated by intravenous injection into tail vein with 500-800 µCi ¹³¹I-Sertraline in a volume of 0.2 mL saline. The rats were sacrificed by decapitation, after narcotization in an ether atmosphere at 5, 20, 45, 90 and 180 min. postinjection. The various organs were removed and weighted. The radioactivity of these organs were counted by Cd(Te) detector equipped with RAD 501 Single Channel Analyzer Instrument and calculated the percent injected radioactivity per gram of tissue. The whole brain was excised quickly, washed into cold saline solution and dissected into brain regions. They were weighted and counted.

RESULT AND DISCUSSION

The obtained RTLC chromatograms are indicated at Table 1. The yield of ¹³¹I-Sertraline was observed to be 85-90%. Then ¹³¹I-Sertraline was separated from unreacted iodine by CSP. Radiochemical purity was 98%. The result of electrophoresis showed that labeled product was neutral. The lipophilicity of ¹³¹I-Sertraline was determined and found 1.1. The uptake of radiopharmaceutical in brain depends on high n-octanol/water ratio and neutral of labeled product, as known (8).

The biodistribution in percentage injected radioactivity per gram of tissue for some selected organs as the mean value of four rats is shown in Figure 2. Figure 2 shows the highest accumulation was observed in liver, heart, kidneys, lung in 20 min. Accumulation was rapid in blood after 5 min. The clearance in the organs was slow depends on decreasing in blood level. Sertraline is extensively metabolized by the liver, excretion of unchanged drug in urine is a minor route of elimination (9). Our results agree with this report, since hepatobiliar and minor renal excretion was seen. According to Kurk and coworker the Sertraline as selective serotonergic reuptake inhibitors (SSRIs), has adverse reactions such as gastrointestinal (especially nausea) and neuropsychiatric (particularly headache and tremor) (10, 11). We also

have seen high uptake in stomach in 90 minutes. The accumulation in thyroid reached to maximum in 20 min. We found similar result (11).

Our results indicated that ^{131}I -Sertraline uptake with the highest activity concentrated in cerebellum, hippocampus, striatum and cortex of brain in 20 minutes (Figure 3). The clearance from these regions of brain is quite slow. The present study examines the effects of acute and chronic administration of the SSRI Sertraline on release of endogenous noradrenalina (NA) in the frontal cortex and hippocampus of the rat using in vivo microdialysis. Acute administration of Sertraline did not significantly alter NA release in either the cortex or the hippocampus (12). Our results agree on the report by Kruk and Pycock who explained that 5-HT receptors in the CNS ascend fibres innervate the basal ganglia, hypothalamus, thalamus, hippocampus, limbic forebrain and areas of the cerebral cortex. 5-HT containing cell bodies in the medulla oblongata give rise to descending axons which terminant in the medulla and the spinal cord (11). According to our results, the uptake in medulla in 5 minutes was high as was reported by Kruk and Pycock (11).

As conclusion, ^{131}I -Sertraline shows a potential as a brain radiopharmaceutical and can be used to obtain SPECT images of brain.

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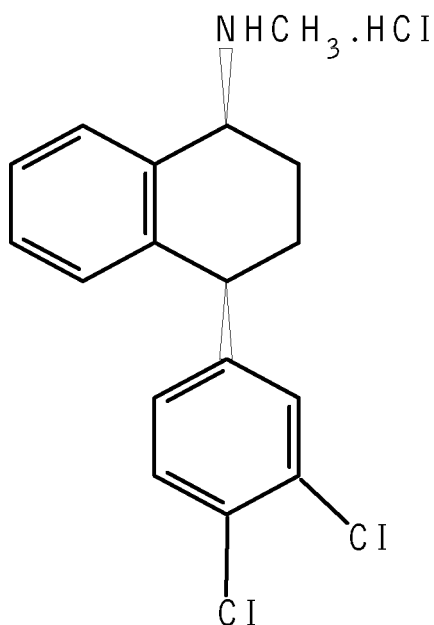


Figure 1: Molecular structure of Sertraline.

TABLE 1. Rf Values

	Solvent 1	Solvent 2
^{131}I Ser	0,82±0,09	0,06± 0,005
^{131}I	0,09±0,002	0,06±0,007
$^{131}\text{I}_2$	1,00±0,001	0,9±0,05

Values presented as mean ± SD. Ser = Sertraline

Solvent 1:n-butanol; Solvent 2:II Isopropyl alcohol/n-butanol/ 0,2N ammonium hydroxide (2/1/1) (v/v).

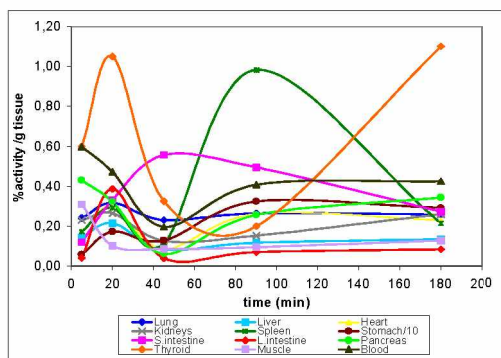


Figure 2: Percent of injected activity of ^{131}I Sertraline per gram tissue, mean value of four rats.

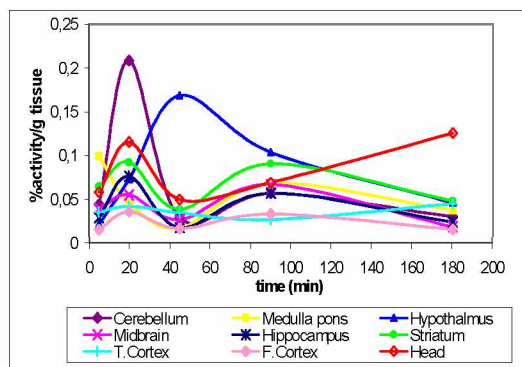


Figure 3: Percent of injected activity of ^{131}I Sertraline per gram brain tissue, mean value of four rats.