A. 研究目的

アルツハイマー型認知症、パーキンソン病等の神経変性疾患の病態は、完全には解明されていないが、神経病理学的所見から、脳の特定部位にβアミロイドが沈着する事やドーパミン神経系の脱落が、発症・進行に大きく影響する事やが明らかになってきている。根治をもたらす治療方法は未だないものの症状を軽減あるいは進行を抑制する治療薬が既に導入されている。このため臨床的見地から早期発見、早期治療が望ましいものの、アルツハイマー型認知症では現在の臨床診断は脳形態画像、症状、経過などから疑い診断に止まり、病態に基づいた確定診断は生体では行えていない。またパーキンソン病は心筋シンチグラム等の画像診断が支持的所見として用いられる様になっているが、症状経過から診断を進める事が多く病態を反映した早期診断が求められている。老年期にみられるうつ病、妄想性障害は未だ十分な病態解明がなされていない。更にこれらの疾患は症候学的には認知症やパーキンソン病との鑑別が必要になることも多く、病態解明や鑑別診断につながるバイオマーカーの開発が求められている。近年、分子イメージングの手法を用いる事で生体内でβアミロイドの存在の確認や評価あるいはドーパミン神経系の機能評価を出来るとする報告がなされ、臨床利用に向けた研究と開発がされている。我々はこれまでの研究で AVID 社が開発したアミロイド分子イメージングのための検査薬[^{18}F]florbetapir を導入し、アルツハイマー病を含む認知症患者群、健常者群、アルツハイマー病のハイリスク群である軽度認知機能障害群を対象に、アミロイド分子イメージングを実施し、有用性を検討した。更にドーパミントランスポーター機能を評価する[^{18}F]FE-PE2I を導入する事で、ドーパミン神経系の評価が精神疾患の病態解明並びに鑑別診断に有用であるかを検討した。

B. 研究方法

薬物試験審査委員会の承認を得たのち、本実験の内容を口頭で説明し、文書により同意の得られた健常者群ならびに妄想性障害、パーキンソン症候群、うつ病を対象とした。妄想性障害、うつ病の診断は国際疾病分類第 10 版に基づいた。パーキンソン症候群は臨床診断に基づき判断をした。状態評価のためミニメンタルステート検査（MMSE）、老年期うつ病評価尺度（GDS）あるいはハミルトンうつ病評価尺度、パーキンソン病統一スケールを実施した。脳器質性病変の鑑別、解析用の脳形態情報を得るために臨床用 PHILIPS 社製 1.5 テスラ MRI 装置 Intera 1.5T Achieve Nova を用いて撮像した。PET 画像は島津製作所製 Eminence SET-3000GCT/X を用いて撮像した。[^{18}F]florbetapir は静脈内に注射し、注射後 50 分から 10 分間のデータを収集し、[^{18}F]FE-PE2I は静脈内に注射後から 60 分間データを収集した。データの解析には PMOD 3.3 (PMOD Technologies Ltd., Zurich,

Switzerland）を使用した。

β アミロイド沈着の評価には、脳剖検の知見を踏まえて Fleisher らにより提唱されている定量化手法を用いた。これは標準脳ならびに統計処理ソフトを用いる事で、前頭葉眼窩野、側頭葉、前部および後部帯状回、頭頂葉ならびに楔前部の領域における集積を皮質ー全小脳比による standard uptake value ratio によりβアミロイド沈着を自動的に数値化するものである。この数字を脳剖検の結果から、アミロイド陰性(SUVRs≤1.08)、アルツハイマー病の病理呈するレベル(SUVRs≥1.17)と 2 つの cut-off 値を示している。今回我々は、SUVRs>1.08 をアミロイド陽性として用いた。

ドーパミントランスポーター機能評価には健常者の[^{18}F]FE-PE2I による線条体における結合能（BP）を求め、年齢との相関を求めた。得られた相関係数を公式として、対象年齢における BP の推定値を求め、以下の式に当てはめる事でドーパミントランスポーター機能の変化を評価した。

BP 変化率(%)＝

（BP 被験者－BP 推定値）/BP 推定値＊100

（倫理面への配慮）

本研究は、ヘルシンキ宣言に基づき倫理面について十分な配慮の上で倫理委員会で承認された説明文書、同意書を用いて文書による説明と同意を得たうえで実施された。本研究で得られたデータは匿名化し、解析を行った。

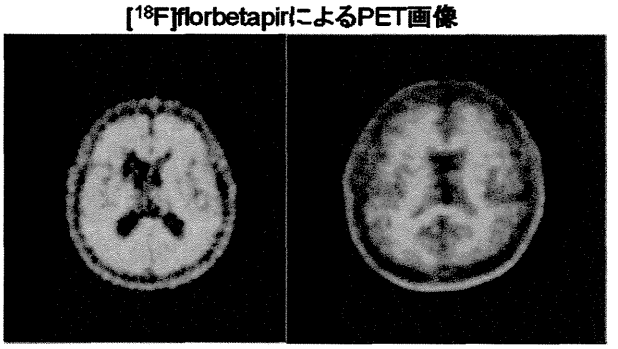
C. 研究結果

健常対照群 36 名、妄想性障害患者群 10 名、パーキンソン症候群患者群 4 名、気分障害患者群 4 名に対して[^{18}F]FE-PE2I を用いてドーパミントランスポーターイメージングを実施した。また妄想性障害患者群の内 7 名に対して[^{18}F]florbetapir を用いたアミロイド分子イメージングを実施した。平均年齢、男女比は以下に示す通りである。

	健常対照群	妄想性障害	パーキンソン症候群	気分障害
N	36	10	4	4
平均年齢	48.5±19.1	75.4±4.6	68.0±11.3	63.3±27.5
男女比	21:15	2:8	1:3	0:4

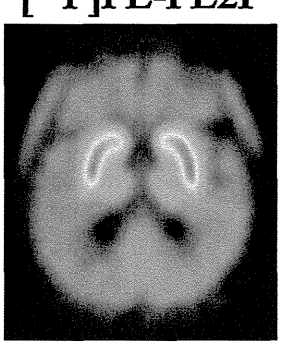
実際の PET 画像を下に示す。

[^{18}F]florbetapirによるPET画像



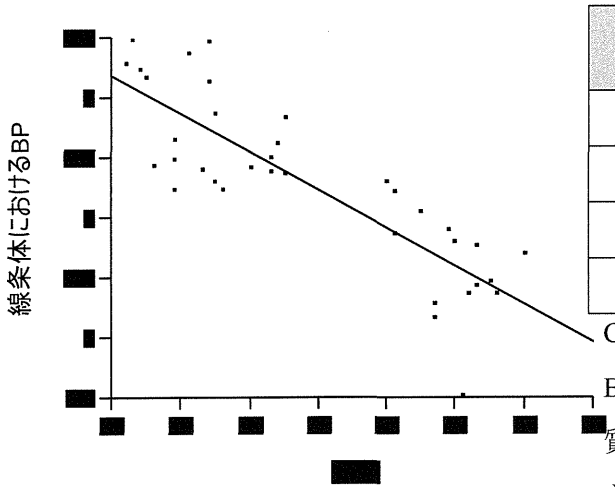
amyloid (+)　　amyloid (-)

[^{18}F]FE-PE2I



（健常対照群）

健常者における BP と年齢関係に関しては以下の通りの結果が得られた。



BP＝-0.03*年齢+4.82 (R^2=0.71, p<0.0001)

（妄想性障害患者群）

妄想性障害患者群を対象とした[^{18}F]florbetapir ならびに[^{18}F]FE-PE2I の結果を以下に示す。

年齢	性別	βアミロイド	ドーパミントランスポーター BP 変化率
81	女	未実施	-24.70%
75	男	陰性	-54.57%
76	女	陽性	-36.44%
74	女	陽性	-10.54%
76	女	陽性	-54.83%
74	女	陰性	未実施
71	女	陽性	-70.14%
69	女	未実施	-2.29%
85	男	陽性	5.53%
73	女	未実施	-5.38%
平均値			**-28.15%**

[^{18}F]FE-PE2I については実施出来た 9 名中 6 名でドーパミントランスポーター機能の 10%以上の低下を示し、平均でも-28.15%の低下を示した。[^{18}F]florbetapir については実施出来た 7 名中 5 名でβアミロイド陽性であった。

（パーキンソン症候群）

	年齢	性別	ドーパミントランスポーターBP 変化率
A	60	女	26.21%
B	73	女	-53.68%
C	84	女	-18.51%
D	55	男	-25.30%

Case A は薬剤性パーキンソン症候群、Case B と C はパーキンソン病、Case D は大脳皮質基底核変性症の臨床診断であった。パーキンソン病患者では BP の低下がある一方で、薬剤性パーキンソン症候群では BP の低下は無かった。Case D では線条体におけるドーパミントランスポーターBP に左右差は見られなかった。

（気分障害患者群）

	年齢	性別	ドーパミントランスポーターBP 変化率		
			通電療法		
			開始前	4 週間後	10 週間後
DP-01	78	女	-38.32%	-43.07%	-47.09%
DP-02	78	女	-12.74%		
DP-03	22	女	-14.20%	-24.87%	
			維持通電療法		
			終了後 4 週	実施直後	
DP-04	75	女	3.11%	-5.89%	

うつ状態にあり通電療法を実施する事になった被験者 3 名ならびにうつ病相に対して 4 週間毎に維持通電療法を実施する事で寛解状態を維持されている 1 名に対して[^{18}F]FE-PE2I を実施し、ドーパミントランスポーター機能を評価した。うつ状態患者における BP は平均-21.75±14.37%と低下していた。ECT を実施するにつれて BP は更に

低下していった。一方寛解状態の患者ではBPは3.11%とほぼ平均値であったが、ECT実施直後は-5.89%に低下した。

D．考察

[^{18}F]FE-PE2I を用いた線条体ドーパミントランスポーター機能評価では、健常者のデータから加齢とともに線条体ドーパミントランスポーター機能が低下する事（10年で約6.2%）が明らかになった。他の検査薬を用いた先行研究でも10年間で約10%程度低下する事が報告されており、ほぼ一致する結果であった。

この結果から得られた推定値を用いて各種疾患におけるドーパミントランスポーター機能評価を行った所、妄想性障害患者では平均28.15%の低下が認められた。妄想性障害におけるドーパミントランスポーター機能の評価はまだ十分に行われていないものの、ドーパミントランスポーター機能低下の結果ドーパミン再取込能力が低下し、シナプス間隙のドーパミン濃度が上昇する事が幻覚妄想状態を引き起こすとする報告もあり、我々の結果はこれを支持するものであった。また同時に行われた[^{18}F]florbetapir では7名中5名でβアミロイド陽性であった事から、老年期にみられる妄想性障害の一部はアルツハイマー型認知症と同様の病態を有している可能性が示された。

パーキンソン症状を呈する疾患では、薬剤性パーキンソン症候群ではドーパミントランスポーター機能の低下はなく、パーキンソン病、大脳皮質基底核変性症ではドーパミントランスポーター機能が低下していた。これらの事から[^{18}F]FE-PE2I による評価はドーパミン神経系の変性を来す疾患において診断に有用である可能性と薬剤性パーキンソン症候群の鑑別診断に有用である可能性が示された。

うつ病ならびに通電療法におけるドーパミントランスポーター機能の役割は未だ不明であるが、ドーパミントランスポーター機能がうつ病相で低下し、抗うつ薬による治療により改善したという報告もある。我々の結果からはうつ病相では、先行研究同様にドーパミントランスポーター機能の低下が示され、寛解状態ではドーパミントランスポーター機能が回復していたという点で先行研究と一致し、うつ病の病態にドーパミントランスポーターが一定の役割を有している可能性が示唆された。通電療法の実施中はドーパミントランスポーター機能が低下し、寛解期ではドーパミントランスポーター機能が回復するという我々の結果は通電療法の治療メカニズムにドーパミントランスポーターが関与している可能性と、うつ病ならびに通電療法の治療評価の指標としてドーパミントランスポーター機能評価が有用である可能性が示唆された。

これらの結果から[^{18}F]FE-PE2I はドーパミントランスポーター機能評価に有用である事が示せた。

今後は更に症例数を増やす事並びに症状

評価尺度との関連を検討する事で病態解明だけでなく、治療効果の指標としての有用性について更に検討を進めて行きたいと考える。

E.結論

本研究により、[^{18}F]FE-PE2I がドーパミントランスポーター機能評価、特にドーパミン神経系の変性を来す疾患の鑑別診断に有用である事が示された。老年期の妄想にはドーパミントランスポーター機能低下が関与している可能性ならびにアルツハイマー型認知症同様に β アミロイドが関与している可能性が示された。更にうつ病の状態ならびに治療効果評価に有用である可能性が示された。今後は更に症例数を増やす事並びに症状評価尺度や予後との関連を検討する事で、治療効果の指標としての有用性について検討を進める事が重要であると考えられた。

F. 健康危険情報 なし

G. 研究発表

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なし

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H.知的財産権の出願・登録状況

なし。

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III 研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

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Ⅳ. 研究成果の刊行物・別刷

Striatal and Extrastriatal Dopamine D_2 Receptor Occupancy by a Novel Antipsychotic, Blonanserin

A PET Study With [^{11}C]Raclopride and [^{11}C]FLB 457 in Schizophrenia

Amane Tateno, MD, PhD, Ryosuke Arakawa, MD, PhD,* Masaki Okumura, MD, PhD,* Hajime Fukuta, MD,* Kazuyoshi Honjo, BPharm,† Keiichi Ishihara, MD, PhD,‡ Hiroshi Nakamura,§ Shin-ichiro Kumita, MD, PhD,|| and Yoshiro Okubo, MD, PhD**

Abstract: Blonanserin is a novel antipsychotic with high affinities for dopamine D_2 and 5-HT_{2A} receptors, and it was recently approved for the treatment of schizophrenia in Japan and Korea. Although double-blind clinical trials have demonstrated that blonanserin has equal efficacy to risperidone, and with a better profile especially with respect to prolactin elevation, its profile of in vivo receptor binding has not been investigated in patients with schizophrenia. Using positron emission tomography (PET), we measured striatal and extrastriatal dopamine D_2 receptor occupancy by blonanserin in 15 patients with schizophrenia treated with fixed doses of blonanserin (ie, 8, 16, and 24 mg/d) for at least 4 weeks before PET scans, and in 15 healthy volunteers. Two PET scans, 1 with [^{11}C]raclopride for the striatum and 1 with [^{11}C]FLB 457 for the temporal cortex and pituitary, were performed on the same day. Striatal dopamine D_2 receptor occupancy by blonanserin was 60.8% (3.0%) [mean (SD)] at 8 mg, 73.4% (4.9%) at 16 mg, and 79.7% (2.3%) at 24 mg. The brain/plasma concentration ratio calculated from D_2 receptor occupancy in the temporal cortex and pituitary was 3.38, indicating good blood-brain barrier permeability. This was the first study to show clinical daily dose amounts of blonanserin occupying dopamine D_2 receptors in patients with schizophrenia. The clinical implications obtained in this study were the optimal therapeutic dose range of 12.9 to 22.1 mg/d of blonanserin required for 70% to 80% dopamine D_2 receptor occupancy in the striatum, and the good blood-brain barrier permeability that suggested a relatively lower risk of hyperprolactinemia.

Key Words: schizophrenia, blonanserin, dopamine D_2 receptor occupancy, positron emission tomography, hyperprolactinemia

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2-(4-Ethyl-1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta [*b*] pyridine, blonanserin, was developed as a novel antipsychotic drug for schizophrenia in Japan and Korea.[1–3] Blonanserin is a relatively new atypical antipsychotic with very high binding affinity for $D_{2,3}$ and 5-HT_{2A} receptors.[4,5] However, unlike some other atypical antipsychotics, blonanserin has a low affinity for other neurotransmitter receptors, including H_1, muscarinic M_1, and $\alpha 1$ adrenergic receptors, which may work to minimize potential adverse effects such as weight gain/sedation, dry mouth, and orthostatic hypotension, respectively. Double-blind clinical trials demonstrated that blonanserin is equal to haloperidol and risperidone about primary end points, and is better than risperidone with respect to a lower risk of prolactin elevation.[6,7]

Neuroimaging studies of dopamine receptor occupancy using positron emission tomography (PET) have elucidated the correlation between dopamine D_2 receptor occupancy and optimal dose of antipsychotic drugs (ie, sufficient antipsychotic effect and lower incidence of adverse effects).[8,9] PET studies investigating different antipsychotic drugs indicated that approximately 70% to 80% dopamine D_2 receptor occupancy in the striatum was required for antipsychotic response, and that occupancy above this range led to extrapyramidal adverse effects.[10–12] The recent systematic review of the association between dopamine D_2 receptor occupancy and clinical effects supported the presence of a therapeutic window, suggesting that a continuing occupancy-response relationship also may exist within this window (60%–78% D_2 occupancy).[13] The clinically approved daily dose of blonanserin has been settled at 8 to 24 mg based on the results of clinical trials. However, the in vivo profile of receptor binding of blonanserin in patients with schizophrenia has not been investigated, and it has not been clarified whether its clinically approved daily dose occupied D_2 receptors in line with the suggested therapeutic window.

Although some antipsychotic drugs have a risk for drug-induced hyperprolactinemia,[14] one of the beneficial characteristics of blonanserin is the lower incidence of hyperprolactinemia.[6] We recently demonstrated that the brain/plasma concentration ratio (B/P ratio) calculated from the dopamine D_2 receptor occupancies in the extrastriatal and pituitary regions reflects the permeability of the blood-brain barrier (BBB), and that it represents a good biomarker for the risk of antipsychotic-induced hyperprolactinemia.[8]

In this study, we investigated (1) the striatal and extrastriatal dopamine D_2 receptor occupancy by the clinically approved daily dose of blonanserin and (2) the B/P ratio of blonanserin to determine the BBB permeability in patients with schizophrenia using PET.

MATERIALS AND METHODS

Subjects and Study Protocol

Fifteen patients diagnosed with schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders,*

From the Departments of *Neuropsychiatry and †Pharmaceutical Service, ‡Clinical Imaging Center for Healthcare, Nippon Medical School, Bunkyo-ku; §Dainippon Sumitomo Pharma Co, Ltd, Chuo-ku; and ||Department of Radiology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan.

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Reprints: Yoshiro Okubo, MD, PhD, Department of Neuropsychiatry, Nippon Medical School, 113-8602, Sendagi 1-1-5, Bunkyo-ku, Tokyo, Japan (e-mail: okubo-y@nms.ac.jp).

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Dr Tateno has full control of all primary data and all of the authors agree to allow the journal to review the data if requested. The conclusions of this article do not reflect the view of endorsement of Dainippon Sumitomo Pharma Co, Ltd.

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Fourth Edition criteria, and 15 healthy volunteers comparable to the patients in age and sex participated in the study. This study was conducted as part of an open-label postmarketing surveillance study of blonanserin in Japan (D4901439; Dainippon Sumitomo Pharma Co, Ltd), and was approved by the ethics committee and review board of Nippon Medical School Hospital, Tokyo, Japan. After complete explanation of the study, written informed consent was obtained from all participants.

Exclusion criteria were the following: (1) subjects treated with electroconvulsive therapy within 90 days before screening; (2) subjects unable to cease anti-Parkinson medication or under the influence of central nervous system depressants; (3) subjects with current or history of severe physical condition, substance abuse, suicide attempt, or suicidal ideation; (4) pregnant or potential pregnancy; and (5) subjects taking other investigational new drugs or clinical trial medicine of postmarketing surveillance. Subject age was limited to between 20 and 64 years.

Inclusion criteria were as follows: (1) subjects were treated with only blonanserin (ie, no other antipsychotic medications) for at least 4 weeks before the study; (2) subjects were treated at the same dosage of 8, 16, or 24 mg/d of blonanserin for at least 2 weeks before the screening; (3) patients took blonanserin twice a day after meals in the morning and evening; and (4) subjects scored less than 120 on the positive and negative syndrome scale (PANSS[15]) at screening.

The use of the following drugs was prohibited from the time of screening to the end of the clinical trial: (1) any other antipsychotics, (2) carbamazepine and methamphetamine hydrochloride, (3) any other drugs affecting digestive organs with dopamine D_2 receptor blocking action, (4) epinephrine, (5) CYP3A4 inhibitor or revulsant, and (6) any other investigational agent or clinical trial medicine of postmarketing surveillance.

Occurrence of extrapyramidal symptoms (EPS) was assessed by the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS).[16] DIEPSS consisted of 8 symptoms of EPS (eg, parkinsonisms, akathisia, dystonia, and dyskinesia) and 1 global assessment of the severity of EPS. In this study, we considered patients with apparent EPS if the global assessment score of DIEPSS was greater than or equal to 2, or if 4 or more symptoms were present at DIEPSS. We also considered patients with apparent hyperprolactinemia defined as plasma prolactin higher than 20.0 ng/mL for men and higher than 40.0 ng/mL for women. Estimation of dopamine D_2 receptor occupancy of patients with well-controlled schizophrenia by blonanserin was scheduled between 2 and 4 weeks after the start, because administration of antipsychotic drugs for at least 6 weeks was recommended by expert consensus guidelines for judging their effectiveness,[17] and there has been the risk of failure to synthesize the radioligand. Because of this possibility of synthesis failure, the study protocol allowed scanning between 12 and 43 days after the start. During the study period, 2 PET scans per patient were performed on the same day, the first scan with [^{11}C]FLB 457 for extrastriatal dopamine D_2 receptor occupancy, and the second scan with [^{11}C]raclopride for striatal dopamine D_2 receptor occupancy. At PET scan day, patients took blonanserin after a meal. The first PET scan was done between 1 and 3 hours after taking blonanserin and the second one between 4.5 and 6.5 hours after. The signal-to-noise ratio by high-affinity radioligand is higher than by low-affinity radioligand. Because dopamine receptor density in the extrastriatal regions is considerably lower than in the striatal region, a high-affinity radioligand such as [^{11}C]FLB 457 is suitable. On the other hand, the time to reach equilibrium condition by [^{11}C]FLB 457 is too long for the half-life of [^{11}C] labeled radioligands, so high-affinity radioligands could cause underestimation of BP_{ND} values especially in regions with high dopamine D_2 receptor densities. Thus, we used different radioligands in this study, [^{11}C]raclopride for a high-density region such as the striatum, and [^{11}C]FLB 457 for a low-density extrastriatal region.[18,19]

Venous blood samples were obtained immediately before tracer injection and after each PET scan to measure the plasma concentration of blonanserin.

PET Procedure

A PET scanner system, Eminence SET-3000GCT/X (Shimadzu Corporation, Kyoto, Japan), was used to measure regional brain radioactivity. Each scan was preceded by a 4-minute transmission scan for attenuation correction using ^{137}Cs. Dynamic PET scanning was performed for 90 minutes after intravenous bolus injection of 212.2 to 249.0 MBq/1.52 (0.25) μg (patients) and 208.8 to 239.1 MBq/1.91 (0.38) μg (healthy volunteers) of [^{11}C]FLB 457. The specific radioactivity of [^{11}C]FLB 457 was 28.3 to 77.6 GBq/μmol [mean (SD), patients, 60.7 (13.6) GBq/μmol; healthy volunteers, 49.1 (11.7) GBq/μmol]. The injected mass of [^{11}C]FLB 457 was 1.25 to 2.76 μg. Dynamic PET scanning was performed for 60 minutes after intravenous bolus injection of 211.1 to 241.8 MBq/0.70 (0.28) μg (patients) and 212.0 to 238.8 MBq/0.97 (0.31) μg (healthy volunteers) of [^{11}C]raclopride. Specific radioactivity of [^{11}C]raclopride was 57.2 to 193.9 GBq/μmol [mean (SD), patients, 140.8 (37.1) GBq/μmol; healthy volunteers, 100.2 (32.8) GBq/μmol]. The injected mass of [^{11}C]raclopride was 0.43 to 1.61 μg. Magnetic resonance (MR) images of the brain were acquired with 1.5 T MR imaging, Intera 1.5 T Achieve Nova (Philips Medical Systems, Best, Netherlands). T_1-weighted MR images were obtained at 1-mm slices.

Data Analysis

All emission scans were reconstructed with a Hanning filter cutoff frequency of 0.4. Regions of interest (ROIs) were defined for the striatum ([^{11}C]raclopride), temporal cortex ([^{11}C]FLB 457), pituitary ([^{11}C]FLB 457), and cerebellar cortex ([^{11}C]raclopride and [^{11}C]FLB 457). ROIs were drawn manually on overlaid coregistered summated PET and MR images of each subject by PMOD (PMOD Technologies Ltd, Zurich, Switzerland). The average values of right and left ROIs were used for the analysis. Dopamine D_2 receptor binding was quantified using a 3-parameter simplified reference tissue model.[20,21] The cerebellum was used as reference region because of its negligible dopamine D_2 receptor density.[22] This model allows estimation of the binding potential (BP_{ND}), which was defined as $f_{ND} \times B_{max} / K_d$, where f_{ND} is the free fraction of ligand in the nondisplaceable tissue compartment, B_{max} is the receptor density, and K_d is the dissociation constant.[23]

Dopamine D_2 receptor occupancy in the striatum and temporal cortex by blonanserin was estimated by the following equation: occupancy (%) = (BP_{base} − BP_{drug}) / BP_{base} × 100, where BP_{base} is BP_{ND} in the drug-free state, and BP_{drug} is BP_{ND} of patients treated with blonanserin.[24–26] In this study, mean BP_{ND} in healthy volunteers was used as BP_{base}, as BP_{ND} in the striatum measured with [^{11}C]raclopride or in the extrastriatal regions (ie, temporal cortex and pituitary) measured with [^{11}C]FLB 457 in patients is not significantly different from that in normal control.[27–29] The same PET procedure and data analysis for BP_{ND} estimation were used for normal subjects and patients. The relationship between dose or plasma concentration of blonanserin and dopamine D_2 receptor occupancy is described by the following equation: occupancy (%) = D / (D + ED_{50}) × 100 or occupancy (%) = C_{plasma} / (C_{plasma} + EC_{50}) × 100, where D is the dose of blonanserin, C_{plasma} is the plasma

concentration of blonanserin, ED_{50} is the dose required to achieve 50% occupancy, and EC_{50} is the plasma concentration required to attain 50% occupancy.[24–26,30] Both ED_{50} and EC_{50} reflect the affinity of antipsychotic drug for dopamine D_2 receptor. In this study, maximum occupancy was fixed at 100%, the same as in previous occupancy studies of risperidone.[26,30]

The B/P ratio was the ratio of drug concentration inside to that outside BBB. Drug concentration in the brain or plasma was calculated by occupancy and IC_{50} as described by the following equation: $C = IC_{50} / ([100 / \text{Occupancy}] - 1)$, in which C is the drug concentration in the brain or plasma. IC_{50} was the drug concentration required to induce 50% occupancy, reflecting the affinity of antipsychotic drug to dopamine D_2 receptor, and the value of IC_{50} was assumed to be the same whether the region was outside or inside BBB. Because the pituitary exists outside BBB and the temporal cortex inside BBB, the B/P ratio can be calculated by the following equation: B/P ratio = $C_{brain} / C_{pituitary} = ([100 / \text{Occupancy}_{pituitary}] - 1) / [(100 / \text{Occupancy}_{temporal}] - 1)$,[8] where C_{brain} is the drug concentration in the vicinity of receptors in the temporal cortex, $C_{pituitary}$ is that in the pituitary, $\text{Occupancy}_{pituitary}$ is the dopamine D_2 receptor occupancy in the pituitary, and $\text{Occupancy}_{temporal}$ is that in the temporal cortex. To calculate the B/P ratio of blonanserin, we used the same area under the time-activity curve (AUC) ratio method as in the previous study to measure dopamine D_2 receptor occupancy in the pituitary.[8] The AUC method does not need the assumptions that are required for the simplified reference tissue model method.[8] The equation of the AUC method was as follows: $BP_{ND} = (AUC_{region} / AUC_{cerebellum}) - 1$. The subscript "region" denotes the pituitary cortex, and an integration interval of 60 to 90 minutes was used for the calculation of AUC. Dopamine D_2 receptor occupancy in the pituitary was estimated by the same equation as for the striatum. The cerebellum was used as reference tissue, given its negligible density of dopamine D_2 receptors.[22]

Measurement of Plasma Concentration of Blonanserin

We measured plasma concentration of blonanserin in the same way as a previous study.[31] Blood samples were collected in heparinized tubes and centrifuged for 10 minutes at 3000 rpm at 4°C. Separated plasma samples were stored at −80°C until analyzed. The plasma concentration of blonanserin was determined by a validated method using high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a target lower limit of quantification of 0.01 ng/mL (JCL Bioassay Corporation, Osaka, Japan).

Statistical Analysis

Correlations between dose or plasma concentration of blonanserin and dopamine D_2 receptor occupancy in the striatum, temporal cortex, and pituitary were assessed. Correlations between striatal occupancy and age or duration of illness were also evaluated. Paired t test was performed to compare (1) dopamine D_2 receptor occupancies between the striatum and temporal cortex and (2) plasma concentrations of blonanserin between the 2 PET scans, with [^{11}C]raclopride and [^{11}C]FLB 457, respectively, in each individual subject. In all tests, a P value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics are shown in Table 1. Fifteen patients [age range, 26–40 years; mean (SD), 32.8 (4.8) years; 8 males, 7 females] and 15 comparable healthy volunteers [age range, 24–54 years; mean (SD), 36.3 (8.3) years; 8 males, 7 females] participated in the study. Average duration of illness was 9.4 (5.7) years and average age at onset of schizophrenia was 23.2 (5.4) years. Average PANSS scores of all patients were 60.2 (19.2) at screening day and 60.1 (18.1) at PET scan day (Table 2). Four patients, one taking 16 mg and three 24 mg, showed EPS (Table 2). Two of 5 patients at 8 mg, 1 of 5 patients at 16 mg, and none of 5 patients at 24 mg met the criteria of hyperprolactinemia at PET scan day (Table 2).

Striatal dopamine D_2 receptor occupancy using [^{11}C]raclopride was 56.9% to 83.7% (Table 3), and mean striatal occupancies were 60.8% (3.0%) at 8 mg/d, 73.4% (4.9%) at 16 mg/d, and 79.7% (2.3%) at 24 mg/d. ED_{50} was 5.53 mg/d ($r = 0.91$) and EC_{50} was 0.17 ng/mL ($r = 0.52$; Fig. 1). Occupancy of dopamine D_2 receptor in the striatum by

TABLE 1. Patient Characteristics

Patient Number	Sex	Age, y	Duration of Illness, y	Age at Onset, y	Dose, mg/d	No. of Days (From Screening to PET Scans)
1	Male	28	0	27	8	40
2	Male	31	7	24	8	61
3	Female	26	5	21	8	214
4	Female	29	2	27	8	47
5	Male	34	8	26	8	43
6	Male	40	13	27	16	61
7	Female	31	8	22	16	181
8	Female	40	16	24	16	40
9	Male	27	8	19	16	43
10	Male	33	16	17	16	47
11	Female	38	13	24	24	133
12	Female	39	2	36	24	66
13	Male	29	14	15	24	151
14	Female	34	10	24	24	54
15	Male	34	19	15	24	42
Mean		32.8	9.4	23.2		82
SD		4.8	5.7	5.4		58.0

TABLE 2. PANSS, EPS, and Plasma Concentration of Prolactin

Patient Number	Sex	PANSS		EPS		Plasma Concentration of Prolactin, ng/mL		Hyperprolactinemia (PET Scan Day)
		Screening Day	PET Scan Day	Screening Day	PET Scan Day	Screening Day	PET Scan Day	
1	Male	34	38	(−)	(−)	18.8	14.4	(−)
2	Male	39	38	(−)	(−)	13.8	16.2	(−)
3	Female	59	59	(−)	(−)	51.1	43.9	(+)
4	Female	75	78	(−)	(−)	80.1	59.2	(+)
5	Male	48	49	(−)	(−)	22.0	10.9	(−)
6	Male	54	55	(−)	(−)	13.7	21.9	(+)
7	Female	83	83	(+)	(+)	29.5	35.5	(−)
8	Female	56	56	(−)	(−)	15.8	19.3	(−)
9	Male	93	85	(−)	(−)	14.8	9.2	(−)
10	Male	86	87	(−)	(−)	19.6	9.4	(−)
11	Female	32	33	(+)	(+)	37.8	35.5	(−)
12	Female	44	43	(−)	(−)	20.9	31.7	(−)
13	Male	72	72	(−)	(−)	7.3	10.5	(−)
14	Female	56	56	(+)	(+)	94.8	26.9	(−)
15	Male	72	69	(+)	(+)	13.2	16.9	(−)
Mean		60.2	60.1			30.2	24.1	
SD		19.2	18.1			25.8	14.6	

blonanserin, calculated from ED_{50}, was 59.1% for 8 mg and 81.3% for 24 mg.

Dopamine D_2 receptor occupancy in the temporal cortex using [^{11}C]FLB 457 was 22.6% to 83.3% (Table 3), and mean occupancies were 46.8% (14.3%) at 8 mg/d, 70.4% (9.2%) at 16 mg/d, and 69.1% (3.3%) at 24 mg/d. ED_{50} was 8.61 mg/d (r = 0.71) and EC_{50} was 0.38 ng/mL (r = 0.13; Fig. 2). The average dopamine D_2 occupancy of [^{11}C]FLB 457 was 9.2% lower (14% at 8 mg, 3% at 16 mg, 10.6% at 24 mg) than that of [^{11}C]raclopride. Although there was a significant difference in dopamine D_2 receptor occupancy between the striatum and temporal cortex at 24 mg (P = 0.002), there were no significant differences in plasma concentrations of blonanserin between the 2 scans (P = 0.50) and in dopamine D_2 receptor occupancy between the striatum and temporal cortex at 8 and 16 mg (P = 0.41 and 0.13, respectively). There was no correlation between striatal occupancy and age or duration of illness. Dopamine D_2 receptor occupancy in the pituitary using [^{11}C]FLB 457 was

TABLE 3. Dopamine D_2 Occupancy in Temporal Cortex, Striatum, and Pituitary

Patient Number	Dose, mg/d	[^{11}C]Raclopride		[^{11}C]FLB 457		
		Plasma Concentration of Blonanserin, ng/mL	Striatum Receptor Occupancy, %	Plasma Concentration of Blonanserin, ng/mL	Temporal Cortex Receptor Occupancy, %	Pituitary Receptor Occupancy, %
1	8	0.174	61.9	0.228	49.5	43.0
2	8	0.286	63.2	0.399	55.5	78.7
3	8	0.215	58.4	0.269	47.4	2.7
4	8	0.161	56.9	0.291	59.2	2.9
5	8	0.452	63.6	0.547	22.6	14.5
Mean (SD)		0.258 (0.119)	60.8 (3.0)	0.347 (0.129)	46.8 (14.3)	28.4 (32.6)
6	16	0.503	67.2	0.878	61.7	23.6
7	16	0.385	70.7	0.669	76.4	36.3
8	16	0.698	79.5	1.261	83.3	62.3
9	16	1.008	72.6	0.877	63.2	58.3
10	16	0.736	77.1	1.035	67.2	56.0
Mean (SD)		0.666 (0.239)	73.4 (4.9)	0.944 (0.220)	70.4 (9.2)	47.3 (16.6)
11	24	0.460	78.4	0.401	68.4	30.4
12	24	1.048	79.0	1.399	71.4	66.7
13	24	0.841	79.4	1.577	63.8	61.9
14	24	0.966	83.7	0.741	72.0	66.7
15	24	1.803	78.2	2.113	69.7	68.1
Mean (SD)		1.024 (0.491)	79.7 (2.3)	1.246 (0.681)	69.1 (3.3)	58.8 (16.0)

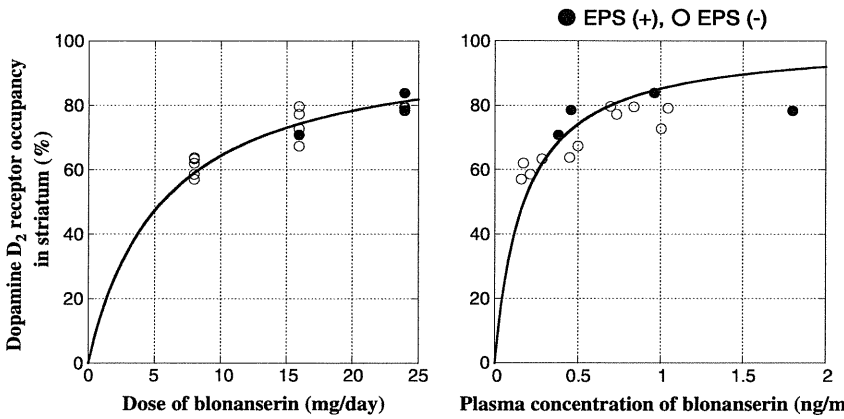

FIGURE 1. Relationship between dopamine D2 receptor occupancy in the striatum and dose or plasma concentration of blonanserin. ED_{50} in the striatum was 5.53 mg/d ($r = 0.91$) and EC_{50} was 0.17 ng/mL ($r = 0.52$) (ED_{50}, dose required to induce 50% occupancy; EC_{50}, plasma concentration required to induce 50% occupancy; EPS, extrapyramidal symptoms).

2.7% to 78.7% (Table 3), and mean occupancies were 28.4% (32.6%) at 8 mg/d, 47.3% (16.6%) at 16 mg/d, and 58.8% (16.0%) at 24 mg/d. ED_{50} was 18.06 mg/d ($r = 0.52$) and EC_{50} was 0.87 ng/mL ($r = 0.60$; Fig. 3). The B/P ratio of blonanserin calculated from our data was 3.88 (5.53).

DISCUSSION

This was the first study to investigate the dopamine D_2 receptor occupancy of the clinical daily dose of blonanserin in patients with schizophrenia. Our study demonstrated the ED_{50} value of the striatal dopamine D_2 receptor occupancy of blonanserin to be 5.53 mg/d and the EC_{50} value 0.17 ng/mL, those of the temporal cortex 8.61 mg/d and 0.38 ng/mL, and those of the pituitary 18.06 mg/d and 0.87 ng/mL. In addition, dopamine D_2 receptor occupancy of the striatum was significantly higher than that of the temporal cortex only at a blonanserin dose of 24 mg.

Before discussing the implications of this study, we should acknowledge its methodological limitation of using mean BP_{ND} in healthy volunteers to calculate the dopamine D_2 receptor occupancy, similarly to a previous study.[32] Although previous studies reported that BP_{ND} in the striatum measured with [^{11}C]raclopride or in the temporal cortex measured with [^{11}C]FLB 457 in patients is not significantly different from that in normal control,[27–29] individual differences in BP_{ND} may lead to potential error in the estimation of dopamine D_2 receptor occupancy.[10] Second, although the dosages of radioactivity of the 2 radioligands were not significantly different, their injected mass doses were significantly higher in the healthy volunteer group than in the patient group. The higher injected mass dose in our study might lower the BP in the healthy volunteers. Third, the effect of the radiolabeled metabolite of [^{11}C]FLB 457 should be considered, although a previous study indicated that a major metabolite of [^{11}C]FLB 457 had very low affinity for dopamine D_2 receptor.[33] Fourth, quantification of BP_{ND} also has methodological limitations. A previous study reported that the cerebellum could be used as a measure of nonspecific binding in the pituitary, because the fully occupied time-activity curve of the pituitary was at almost the same level as the cerebellum.[8] Therefore, we used the cerebellum as reference region in this study. However, nonspecific binding in the pituitary may not be the same as that of brain parenchyma.

We know from previous PET studies that around 70% to 80% occupancy in the striatum is required for a clinical response and that more than approximately 80% occupancy causes extrapyramidal adverse effects. The occupancy range of dopamine D_2 receptors in the striatum by 8 to 24 mg/d of blonanserin was 59.1% to 81.3%. The dose range required for the range of optimal dopamine D_2 receptor occupancy in the

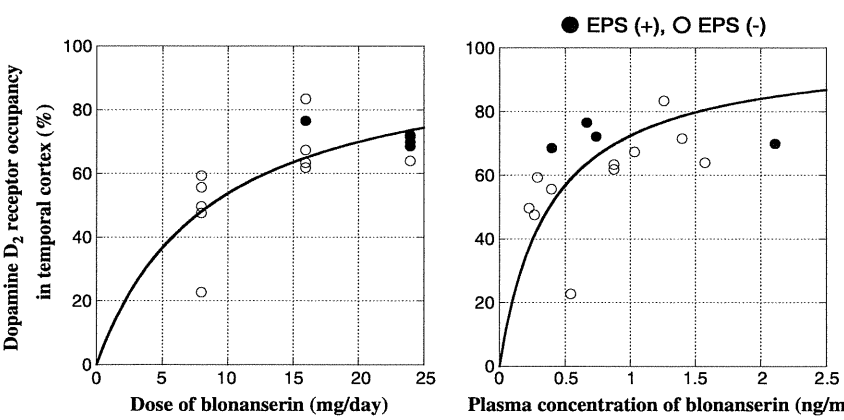

FIGURE 2. Relationship between dopamine D_2 receptor occupancy in the temporal cortex and dose or plasma concentration of blonanserin. ED_{50} in the temporal cortex was 8.61 mg/d ($r = 0.71$) and EC_{50} was 0.38 ng/mL ($r = 0.13$) (ED_{50}, dose required to induce 50% occupancy; EC_{50}, plasma concentration required to induce 50% occupancy).

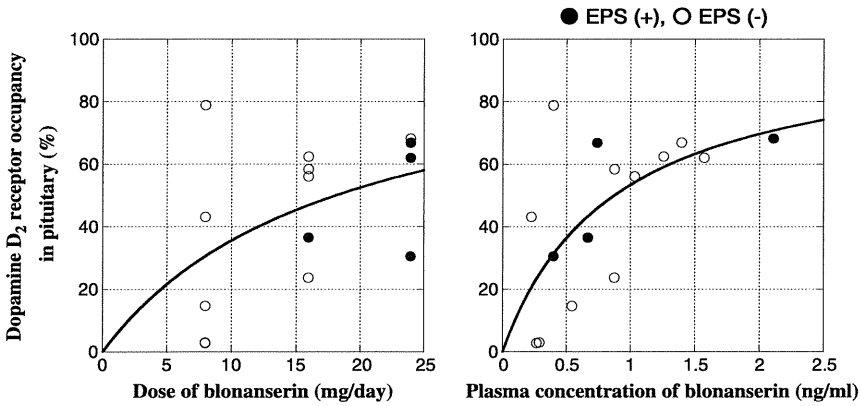

FIGURE 3. Relationship between dopamine D_2 receptor occupancy in the pituitary and dose or plasma concentration of blonanserin. ED_{50} in the pituitary was 18.06 mg/d ($r = 0.52$) and EC_{50} was 0.87 ng/mL ($r = 0.60$) (ED_{50}, dose required to induce 50% occupancy; EC_{50}, plasma concentration required to induce 50% occupancy).

striatum, calculated from ED_{50} and EC_{50}, was 12.9 to 22.1 mg/d and 0.44 to 0.76 ng/mL, respectively. The corresponding dose range to another therapeutic window of 60% to 78% D_2 occupancy suggested by a systematic review[13] was 8.3 to 19.6 mg/d. Thus, dopamine D_2 receptors of patients with schizophrenia might be almost optimally occupied when they are treated with the approved clinical daily dose range of 8 to 24 mg/d of blonanserin. However, more than 20 mg/d of blonanserin may have a higher incidence of EPS than a lower dose.

From another viewpoint, it should be noted that the dose-setting for blonanserin based on clinical trials in which a larger population of patients needed to be included showed good consistency with the optimal dose suggested by D_2 receptor occupancies investigated in a small number of patients. This suggested the validity and usefulness of dose-setting for antipsychotic drugs using PET.

Our results that patients taking 24 mg of blonanserin had an average dopamine D_2 occupancy in the striatum of approximately 80% and that 3 of 5 patients showed apparent EPS seem to be consistent with the hypothesis that more than approximately 80% occupancy causes extrapyramidal adverse effects. When examining striatal dopamine D_2 receptor occupancy in patients with apparent EPS individually, 3 patients had approximately 80%, but 1 patient had approximately 70%. Several factors such as sensitivity to antipsychotics, effect of previous medications, drug interaction, etc, might explain this result, but at this time it cannot be definitively stated why some patients with lower dopamine D_2 receptor occupancy in the striatum show EPS. Further study on the sensitivity to antipsychotics might one day answer this question.

Blonanserin has a high affinity for D_3 receptors as well as D_2 receptors [K_i value is 0.494 (0.137) nmol/L for D_3 receptors, and 0.142 (0.002) nmol/L for D_2 receptors],[5] and the D_2/D_3 affinity ratio was 0.287. This D_2/D_3 affinity ratio was higher than that of risperidone (0.157) and lower than those of quetiapine and ziprasidone (2.059 and 2.174, respectively).[34] Although the D_2/D_3 affinity ratio should not be neglected, in this study we could not distinguish dopamine D3 receptor binding from dopamine D_2 receptor binding by blonanserin, because both [^{11}C]raclopride and [^{11}C]FLB 457 also have affinity for dopamine D_3 receptors.

Interestingly, some PET studies reported that dopamine D_2 receptor occupancy in the extrastriatum was higher than in the striatum among atypical antipsychotics[35–37] and proposed the concept of "limbic selectivity" for the characteristics of atypical antipsychotics. We compared the striatal and extrastriatal dopamine D_2 receptors using different radioligands, [^{11}C]raclopride for the striatum and [^{11}C]FLB 457 for the extrastriatum, and we demonstrated that the average dopamine D_2 occupancy in the temporal cortex measured by [^{11}C]FLB 457 was 9.2% lower than that in the striatum measured by [^{11}C]raclopride. The dissociation constant K_d, indicating affinity for receptors in the living human brain, was quite different between [^{11}C]raclopride and [^{11}C]FLB 457. Although non-negligible specific binding in the cerebellum by [^{11}C]FLB 457 and differences in K_d value between 2 different radioligands cause systematic errors in occupancy,[22,38] the use of 2 tracers with different affinities, [^{11}C]raclopride and [^{11}C]FLB 457, must be superior compared with the use of 1 tracer to determine the occupancy in both the striatum and extrastriatum. Although direct comparisons of dopamine D_2 receptor occupancy between striatal and extrastriatal regions determined by different tracers may not be appropriate due to systematic errors in occupancy for [^{11}C]FLB 457 studies,[39] our findings suggested that the concept of "limbic selectivity" might not be applicable to blonanserin. However, the present study has demonstrated that dopamine D_2 receptor occupancy measured by [^{11}C]FLB 457 was lower than that by [^{11}C]raclopride, because the cerebellum has a somewhat higher affinity for [^{11}C]FLB 457 and non-negligible specific binding in the cerebellum might cause an underestimation of dopamine D_2 receptor occupancy by [^{11}C]FLB 457.[40,41] This possibility made it unclear whether the "limbic selectivity" of blonanserin should be excluded or not.

Another important finding was that the B/P ratio of blonanserin calculated from our data was 3.88 (5.53). Although it is difficult to compare it directly with the data for other antipsychotic drugs from our previous study,[8] blonanserin showed the highest B/P value in comparison to haloperidol [2.40 (2.40)], olanzapine [2.70 (1.84)], risperidone [1.61 (1.00)], and sulpiride [0.34 (0.42)] (data from Arakawa et al[8]). Other valuable findings from our study were that the average D_2 occupancy in the pituitary was less than 60% even at maximum dose, and ED_{50} in the pituitary was 2 times larger than in the temporal cortex. The prevalence of hyperprolactinemia by blonanserin was 20.0%. When we applied the same criteria of hyperprolactinemia in this study as in the previous study,[8] this prevalence was 20% for haloperidol, 14.3% for olanzapine, 57.1% for risperidone, and 100.0% for sulpiride. These findings might explain why the level of plasma concentration of prolactin did not elevate during the study, and support the hypothesis

that blonanserin shows relatively low risk of hyperprolactinemia as compared to other antipsychotics. These data were consistent with a previous study reporting that the blood prolactin level was lower with blonanserin as compared to risperidone.[6,7]

In conclusion, the results of dopamine D_2 receptor occupancy in the striatum by the approved clinical daily dose of blonanserin indicated that the optimal therapeutic dose of blonanserin for 70% to 80% D_2 occupancy was 12.9 to 22.1 mg/d. Blonanserin, which showed good permeability of BBB as expressed by a higher B/P ratio compared to other antipsychotics, poses a relatively low risk for hyperprolactinemia.

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