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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Adenosine A_{2A} Receptor Occupancy by Long-Term Istradefylline Administration in Parkinson's Disease

Istradefylline, an adenosine A_{2A} receptor ($A_{2A}R$) antagonist, has been used in Japan since 2013 as an adjunct to levodopa to alleviate *off* episodes in patients with Parkinson's disease (PD) and was approved by the US Food and Drug Administration in 2019.[1,2] Currently, once-daily oral administration of 20 or 40 mg is recommended. To understand the pharmacological effects of istradefylline, we measured $A_{2A}R$ availability using ^{11}C-preladenant positron emission tomography (PET) before and after single administration of istradefylline in patients with PD and found that occupancy rates of $A_{2A}Rs$ in the striatum by single administration of 20 and 40 mg were 39.5% and 52.1%, respectively.[3] The major drawback of our previous study is that daily administration of istradefylline can increase its baseline plasma concentration, leading to increasing occupancy rates of $A_{2A}Rs$ because the plasma elimination half-life of istradefylline is long (57.09 ± 31.51 hours). The aim of this study was to resolve the drawback of our previous study by recalculating occupancy rates of $A_{2A}Rs$ after long-term administration of istradefylline in patients with PD.

A total of 4 patients with PD aged 78 to 82 years under medication therapy with 2 or more antiparkinsonian drugs including levodopa underwent a total of 2 ^{11}C-preladenant PET to measure $A_{2A}R$ availability on 2 occasions: at baseline and more than 2 months after starting daily administration of istradefylline 20 or 40 mg (both n = 2). Thus, the daily dose of istradefylline was set at 20 mg for patients 1 and 2 and 40 mg for patients 3 and 4.

After processing PET images as described previously,[3] binding potential (BP_{ND}) was measured as an index of $A_{2A}R$ availability. $A_{2A}R$ occupancy upon istradefylline administration was calculated using the following equation: occupancy (%) = $100 \times [(BP_{ND}$ at baseline) – (BP_{ND} at istradefylline-loading)] / (BP_{ND} at baseline). The relationship between $A_{2A}R$ occupancy and dose of istradefylline was modeled using the following equation: occupancy (%) = $100 \times [D / (D + ED_{50})]$, where D refers to dose of istradefylline and ED_{50} refers to the level resulting in 50% receptor occupancy.

The striatal BP_{ND} values at baseline and more than 2 months after starting daily administration of istradefylline were 3.035 and 0.789 in patient 1 (20 mg loading), 2.759 and 0.825 in patient 2 (20 mg loading), 3.259 and 0.359 in patient 3 (40 mg loading), and 3.068 and 0.490 in patient 4 (40 mg loading), as shown in BP_{ND} maps (Fig. 1A–D). The $A_{2A}R$ occupancy was 74.0%, 70.1%, 89.0%, and 84.0%, in patients 1, 2, 3, and 4, respectively. The dose-occupancy curve estimated that ED_{50} was 7.28 mg (Fig. 1E).

In conclusion, the present study confirmed that istradefylline dose-dependently binds to $A_{2A}Rs$ with doses increasing from 20 to 40 mg in patients with PD under levodopa therapy and found new observations that the mean occupancy rates of $A_{2A}Rs$ in the striatum after long-term administration of istradefylline at 20 and 40 mg doses were 72.1% and 86.5%, respectively, and ED_{50} was 7.28 mg. A more sufficient occupancy of $A_{2A}Rs$ can be obtained by long-term administration of istradefylline than by single administration.

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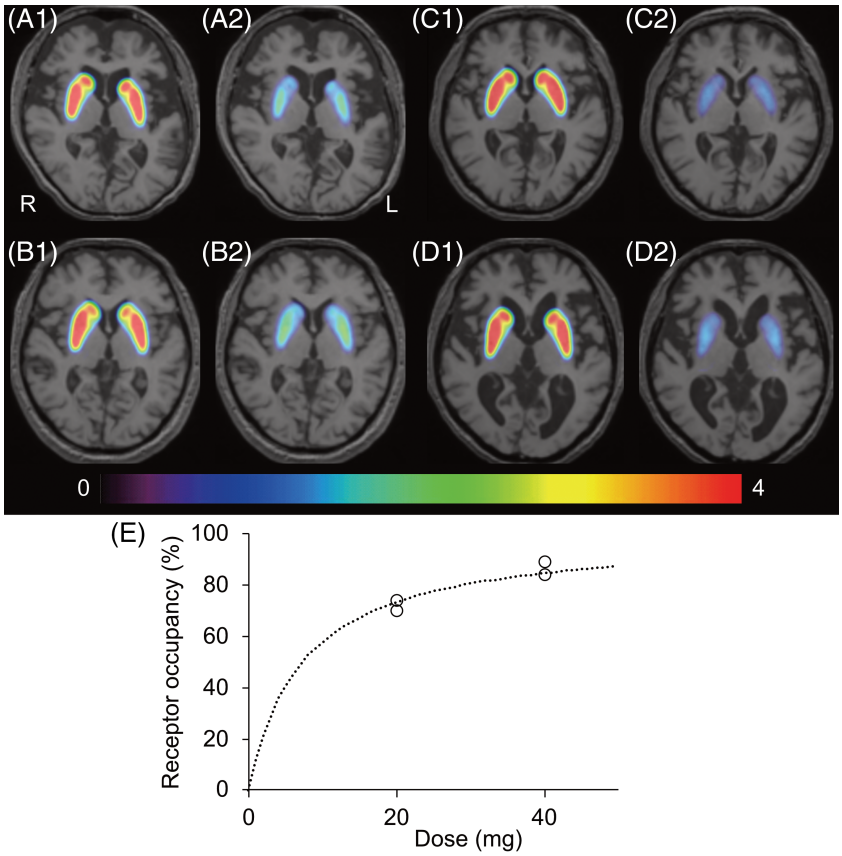

FIG. 1. BP_{ND} maps in 4 patients with PD and relationship between adenosine A_{2A} receptor occupancy and dose of istradefylline. BP_{ND} maps of adenosine A_{2A} availability in patients 1 (**A**), 2 (**B**), 3 (**C**), and 4 (**D**) are displayed on structural magnetic resoannce imaging as follows: the baseline (A1, B1, C1, and D1), istradefylline 20 mg loading (A2 and B2), and istradefylline 40 mg loading (C2 and D2). The rainbow-colored scale represents the magnitude of BP_{ND} values. The dashed curve (**E**) was modeled using the following equation: occupancy (%) = $100 \times [D/(D + ED_{50})]$, where D refers to dose of istradefylline and ED_{50} refers to the level resulting in 50% receptor occupancy. BP_{ND}, binding potential; L, left; PD, Parkinson's disease; R, right. [Color figure can be viewed at wileyonlinelibrary.com]

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