Istradefylline Administration in Parkinson’s Disease

Istradefylline, an adenosine A2A receptor (A2AR) 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 A2AR availability using 11C-preladenant positron emission tomography (PET) before and after single administration of istradefylline in patients with PD and found that occupancy rates of A2ARs 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 A2ARs 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 A2ARs 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 11C-preladenant PET to measure A2AR 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 (BPND) was measured as an index of A2AR availability. A2AR occupancy upon istradefylline administration was calculated using the following equation: occupancy (%) = 100 × [(BPND at baseline) – (BPND at istradefylline-loading)] / (BPND at baseline). The relationship between A2AR occupancy and dose of istradefylline was modeled using the following equation: occupancy (%) = 100 × [D / (D + ED50)], where D refers to dose of istradefylline and ED50 refers to the level resulting in 50% receptor occupancy.

The striatal BPND 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 BPND maps (Fig. 1A–D). The A2AR 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 ED50 was 7.28 mg (Fig. 1E).

In conclusion, the present study confirmed that istradefylline dose-dependently binds to A2ARs 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 A2ARs in the striatum after long-term administration of istradefylline at 20 and 40 mg doses were 72.1% and 86.5%, respectively, and ED50 was 7.28 mg. A more sufficient occupancy of A2ARs can be obtained by long-term administration of istradefylline than by single administration.

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