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An evaluation of istradefylline treatment on Parkinsonian motor and cognitive deficits in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated macaque models

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ABSTRACT

Istradefylline (KW-6002), an adenosine A2A receptor antagonist, is used adjunct with optimal doses of L-3,4-dihydroxyphenylalanine (L-DOPA) to extend on-time in Parkinson's disease (PD) patients experiencing motor fluctuations. Clinical application of istradefylline for the management of other L-DOPA-induced complications, both motor and non-motor related (i.e. dyskinesia and cognitive impairments), remains to be determined. In this study, acute effects of istradefylline (60–100 mg/kg) alone, or with optimal and sub-optimal doses of L-DOPA, were evaluated in two monkey models of PD (i) the gold-standard 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated macaque model of parkinsonian and dyskinetic motor symptoms and (ii) the chronic low dose (CLD) MPTP-treated macaque model of cognitive (working memory and attentional) deficits. Behavioural analyses in L-DOPA-primed MPTP-treated macaques showed that istradefylline alone specifically alleviated postural deficits. When combined with an optimal L-DOPA treatment dose, istradefylline increased on-time, enhanced therapeutic effects on bradykinesia and locomotion, but exacerbated dyskinesia. Istradefylline treatment at specific doses with sub-optimal L-DOPA specifically alleviated bradykinesia. Cognitive assessments in CLD MPTP-treated macaques showed that the attentional and working memory deficits caused by L-DOPA were lowered after istradefylline administration. Taken together, these data support a broader clinical use of istradefylline as an adjunct treatment in PD, where specific treatment combinations can be utilised to manage various L-DOPA-induced complications, which importantly, maintain a desired anti-parkinsonian response.

1. Introduction

The most common treatment for Parkinson's disease (PD) patients remains to be the dopamine precursor, L-3,4-dihydroxyphenylalanine (L-DOPA) despite the frequent development of severe complications with repeated use, which include on-off fluctuations of therapeutic action (Shoulson et al., 1975), dyskinesia (Ahlskog and Muenter, 2001) and, the unpredictable effects on PD-related cognitive dysfunction, such as attention shifting and working memory (Gotham et al., 1988; Brown and Marsden, 1990; Owen et al., 1992).

Istradefylline (KW-6002), a selective adenosine A2A antagonist, recently approved in Japan for clinical use as an adjunct treatment in PD for the management of L-DOPA-induced motor complications (Dungo and Deeks, 2013; Pinna, 2014), has so far been utilised for extending the therapeutic action of L-DOPA, known as 'on-time'. With similar efficacy to clinically used dopaminergic metabolising enzyme inhibitors (Rascol et al., 2005; Lees, 2008), istradefylline (20–60 mg/day) when given with optimal doses of L-DOPA increases daily on-time in advanced PD patients by approximately

Abbreviations: CLD, Chronic low dose; CPT, Continuous performance task; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NHP, Non-human primate; PD, Parkinson's disease; LID, L-DOPA-induced dyskinesia; L-DOPA, L-3,4-dihydroxyphenylalanine; VDR, Variable delay response.

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1 hour (Hauser et al., 2003; Mizuno and Kondo, 2013). However, such treatment regimens commonly exacerbate the expression of certain dyskinesia (Chen et al., 2013; Kondo and Mizuno, 2015), of which may be 'non-troublesome' as described by some PD patients (Lewitt et al., 2008; Stacy et al., 2008). Interestingly, preclinical studies have shown that istradefylline also mediates 'L-DOPA sparing' effects i.e. maintained anti-parkinsonian response when sub-optimal L-DOPA doses are given (Grondin et al., 1999; Kanda et al., 2000) but further exploration into this treatment regimen is required. This includes characterising the effects of istradefylline with different L-DOPA dose combinations on PD and LID motor symptoms, as well as therapeutic on-time, for elucidating the most effective treatment strategy for clinical application (Bara-Jimenez et al., 2003).

'Frontal like' cognitive deficits in PD, on aspects of attention (Flowers and Robertson, 1985; Downes et al., 1989; Sharpe, 1990) and executive function, that is planning and cognitive flexibility (Owen et al., 1993; Brown and Marsden, 1988; Cooper et al., 1991), are also major unmet clinical needs that significantly impact the quality of patient life (Schrag et al., 2000; Chaudhuri et al., 2006). Such deficits can be found present throughout the disease time course (Lees and Smith, 1983; Levin et al., 1989; Owen et al., 1993) and increase in incidence (10–80%) from early to advanced disease stages (Williams-Gray et al., 2007; Hely et al., 2008; Muslimovic et al., 2009). While L-DOPA treatment alleviates parkinsonian motor disabilities by restoring dopamine depletion in regions of the striatum related to motor function, cognitive deficits are often worsened (Gotham et al., 1988; Kulisevsky et al., 1996), possibly from dopamine influx to cortical areas related to cognitive function (Swainson et al., 2000; Cools, 2006). Interestingly, several preclinical studies have suggested that specific blockade of adenosine A2A receptors within the basal ganglia that are localised to enkephalinergic neurons (Schiffmann et al., 1991a; Schiffmann and Vanderhaeghen, 1993), which form specific pathways along corticostriatal-thalamocortical loops (Alexander et al., 1986; Alexander and Crutcher, 1990), may be beneficial for cognitive improvement in PD (Gevaerd et al., 2001; Prediger et al., 2005; Takahashi et al., 2008). In this context, the potential use of istradefylline treatment, for antagonism of A2A receptors, in cognitive dysfunction in PD, remains to be explored.

In this study, we investigated the behavioural effects of istradefylline treatment on motor and cognitive deficits in parkinsonian monkeys, in order to determine efficacious treatment strategies in PD for clinical use. We first evaluated the effects of istradefylline alone, or in combination with optimal and sub-optimal doses of L-DOPA, on therapeutic on-time and motor symptoms in the gold standard MPTP-treated macaque model of PD and LID. Thereafter, the effects of these combinative treatment regimens were evaluated on measurable PD-related cognitive deficits in chronic low dose (CLD) MPTP-treated monkeys.

2. Methods

Experimental procedures were conducted under the regulations set by the European Communities Council Directive 24 November 1986 (86/609/EEC), approved by the Institute of Laboratory Animal Science Ethical Committee (Chinese Academy of Medical Sciences, Beijing, China), and completed in an AAALAC-accredited facility.

2.1. Animals

Captive bred monkeys (*Macaca fascicularis;* Xieerxin, Beijing, mean weight = 4.2 kg; mean age = 6.1 years) were individually housed in cages under controlled conditions (humidity, temperature, 12 hour (h) light/dark cycle with lights on from 8:00 a.m.–8:00 p.m.) and cared for by skilled veterinarians and technicians.

2.2. Experimental monkey models of PD

Two experimental non-human primate (nhps) models of PD were used to fully evaluate the treatment effects of istradefylline on (i) motor and (ii) cognitive deficits.

2.2.1. Group 1 – induction of PD and LID motor symptoms

The gold-standard MPTP-treated macaque model of PD and LID was used to characterise the treatment effects on motor symptoms (Bezard et al., 2003; Ko et al., 2014b). Female monkeys (n = 6) received daily MPTP hydrochloride injections (0.2 mg/kg, intravenous; i.v.) until parkinsonian motor signs appeared, as previously described on several occasions (Porras et al., 2012; Ko et al., 2014a). Following the stabilisation of PD motor impairments, animals received L-DOPA treatment (Madopar®, Roche, L-DOPA/Carbidopa, 4:1 ratio; range of 8–18 mg/kg) at an individually titrated dose for maximal reversal of PD motor symptoms and priming of LID, which was defined as the 100% dose (mean = 17 mg/kg). Animals were treated daily with 100% L-DOPA for 4–5 months for the induction of reproducible dyskinesia as previously described on multiple occasions (Aubert et al., 2005; Guigoni et al., 2005; Gold et al., 2007; Porras et al., 2012). This was followed with twice weekly L-DOPA treatment for maintaining a consistent severity of dyskinesia.

2.2.2. Group 2 – induction of PD-related cognitive deficits

The chronic low dose (CLD) MPTP-treated macaque model of PD was utilised to determine drug treatment effects on PD-related cognitive dysfunction. Male monkeys (n = 6) were trained to achieve a stable baseline performance on cognitive tests, prior to being rendered parkinsonian, as previously described (Schneider and Kovelowski, 1990; Schneider et al., 1999, 2013). Briefly, animals received CLD MPTP injections (at a range of 0.05–0.25 mg/kg; i.v.) two-three times per week for up to 15 months for the induction of stable cognitive and motor deficits. Initial MPTP injections for each animal continued until a consistent 15% reduction in baseline cognitive task performances was seen. Thereafter, MPTP injections continued at an increased dose over several weeks until parkinsonian motor signs reached a mild to moderate severity. A varied amount of total MPTP (range 99.2–140.9 mg) was given between animals for induction of similar cognitive deficits, due to individual differences in the sensitivity to the neurotoxin, as previously reported (Schneider and Kovelowski, 1990; Schneider et al., 1999, 2003). Animals received individually titrated doses of L-DOPA (at a range of 10–25 mg/kg; mean dose = 20 mg/kg) for the reversal of PD motor signs but were not primed for dyskinesia.

2.3. Drug treatment

All test treatments were administered at a volume of 2 ml/kg. Istradefylline (60, 75, 100 mg/kg) was administered in combination with vehicle, optimal (100%; mean = 17 mg/kg; range of 10–25 mg/kg) or sub-optimal (50%; mean = 8.5 mg/kg; range of 5–12.5 mg/kg) L-DOPA doses in motor behavioural tests. In drug tests on cognition task performance, istradefylline was tested in combination with high and low doses of L-DOPA, defined as the L-DOPA dose that improved PD motor signs of CLD MPTP-treated nhps by 80% and 50%, respectively.

2.4. Behavioural analysis

2.4.1. Motor

Immediately following drug administration, animals were