Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol13Issue3abst200P.pdf

A study on the effect of opicapone on the levodopa induced rotational behaviour in 6-OHDAhemiparkinsonian rats

Selective inhibition of catechol-O-methyltransferase (COMT) is of central importance in levodopa therapy of Parkinson's disease; however, the currently available inhibitors like entacapone (ENTA) present drawbacks that limit their use. Opicapone [2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide] (OPC) is a third generation COMT inhibitor developed to overcome those limitations. This study evaluated the effect of OPC and ENTA on levodopa induced rotational behaviour of hemiparkinsonian rats. Wistar rats (N=50) were rendered hemi-parkinsonian by injection of 6-hydroxydopamine (6-OHDAHBr, 5 µg/µl) into the lateral medial forebrain bundle(AP -4.4mm; ML±1.0 mm; DV: -7.8 mm from dura matter) (1). Three weeks after lesionioning animals that showed a positive rotational response to apomorphine were given either OPC(3 mg/Kg, p.o.) once daily for three consecutive days or ENTA(3 mg/Kg, p.o.) twice daily for three consecutive days and again 30 minutes before levodopa. On the fourth day rats were given a single dose of levodopa:benserazide (24:6 mg/Kg, i.p.) and rotational behaviour was evaluated. At the end of the study animals were sacrificed with an overdose of sodium pentobarbital. Blood and liver samples were collected at various time points from a group of animals (sham, non-lesioned animals, N=18) subjected to the same drug treatments. Plasma was used for the quantification of levodopa and 3-O-methyldopa and liver samples were used for COMT assay. Data are given as mean±SEM (n animals) and analysis was performed using one way ANOVA followed by Dunnett's multiple comparisons test.Animal experiments were conducted in strict adherence to the 2010/63/EU European directive on the protection of animals used for scientific purposes and the Portuguese law on animal welfare. In hemiparkinsonian animals pre-treatment with OPCor ENTA enhanced the number of contralateral turns induced by levodopa, and this increase was greater in OPC treated animals (vehicle: 1748±204, n=9; OPC: 2744±692, n=5; ENTA: 1811±359, n=5, total number of contra lateral rotations). OPC and ENTA significantly increased the area under the concentration-time curve (AUC) of plasma levodopa (vehicle: 8055±664, n=6; OPC: 11846±1270*, n=5; ENTA: 11818±896*, n=6, arbitrary units, $P<0.05$ compared to vehicle) and decreased plasma 3-O-methyldopa AUC as compared to vehicle treated animals (vehicle: 26987±1819, n=6; OPC: 11525±2497*, n=5; ENTA: 18993±4262, n=6, arbitrary units, $P<0.05$ compared to vehicle values). Liver COMT was significantly inhibited over the course of the experiment in OPC treated animals, but only transiently inhibited in ENTA treated animals.

Table 1- Effect of OPC and ENTA on liver COMT activity (nmol/mg prot/h). *P<0.05 compared to vehicle.

time (min)	Vehicle	OPC	ENTA
10	49.84±4.84 (n=6)	15.81±1.12* (n=5)	21.90±3.70* (n=6)
30	41.90±3.02 (n=6)	21.25±4.05* (n=5)	18.47±2.52* (n=6)
60	41.05±5.15 (n=6)	19.76±2.03* (n=5)	26.68±2.59* (n=6)
120	44.29±3.73 (n=6)	20.26±2.76* (n=5)	26.04±2.12* (n=6)
240	48.16±5.07 (n=6)	17.65±5.35* (n=5)	31.46±5.59 (n=6)
360	50.18±5.97 (n=6)	17.04±5.03* (n=5)	42.08±4.31 (n=6)

In hemiparkinsonian rats, pre-treatment with opicapone or entacapone before levodopa/benserazide, increased the rotational behaviour and this effect was more pronounced in opicapone treated rats.

(1) Torres EM *et al* (2011). *J Neurosci Methods*. **200**: 29–35.