Motor function in Parkinson's disease during 16h treatment with intravenously (DIZ101), subcutaneously (DIZ102), or intestinally (LCIG) infused levodopa

Filip Bergquist[1,2], Mats Ehrnebo[3], Dag Nyholm[4], Anders Johansson[5], Fredrik Lundin[6], Per Odin[7], Per Svenningsson[5], Nil Dizdar[6], Elias Eriksson[1]

1) Dept of Pharmacology, University of Gothenburg, 2) Neurology, Sahlgrenska University Hospital 3) Pharm Assist Sweden AB 4) Dept of Neuroscience, Uppsala University 5) Dept of Clinical Neurosciences, Karolinska Institutet 6) Dept of Biomedical and Clinical Sciences, Linköping University 7) Neurology, Dept of Clinical Sciences, Lund University

UNIVERSITY OF GOTHENBURG

Background and objectives

LCIG is efficacious for treating motor fluctuations in Parkinson's disease. Pharmacokinetic data indicate stable blood concentrations of levodopa, equivalent with those following LCIG, during treatment with DIZ101 and DIZ102.[1] The carbidopa blood concentration was however four times higher than with LCIG.[1] The objective of this study was to investigate if the efficacy of DIZ101 and DIZ102 is reduced compared to LCIG, indicating a negative effect of high carbidopa levels by inhibition of the conversion of levodopa to dopamine in the brain.

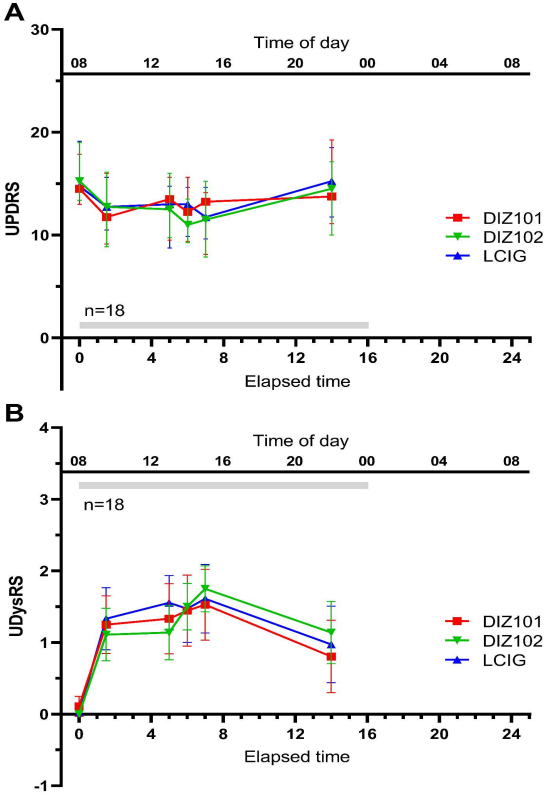

Figure 1: Video ratings of UPDRS-items 23, 25-27, 29 and 31 (A) and the intensity of dyskinesia according to UDysRS (B).

Method

DIZ101, DIZ102 and LCIG were compared in a randomized, 3-period crossover, open-label, multicenter trial where 18 patients with Parkinson's disease completed all treatments. Formulations were infused for 16 hours. The effects of the treatments on motor symptoms were blindedly assessed before and during infusions by repeated UPDRS, UdysRS and Treatment Response Scale (TRS) video rating of a subset of UPDRS III items and by concurrent passive accelerometry recordings with the Parkinson Kinetigraph (PKG) over 24h.

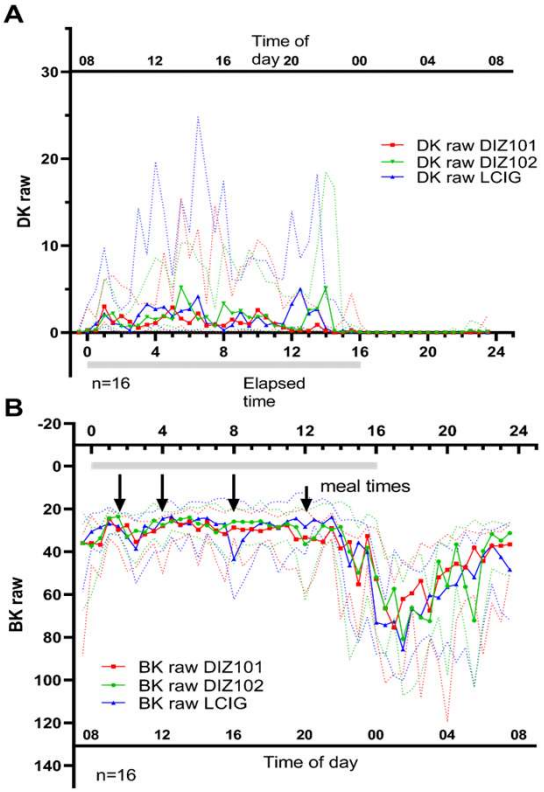

Figure 2: Unfiltered 30 minutes medians of DK (A) and BK (B) scores from PKG recordings of spontaneous motor activity during and after infusions.

Results

Pharmacokinetic results have been published previously.[1] After 1.5h of infusion mean (SEM) UPDRS scores were reduced by 2.6 (0.98) points (17%) with DIZ101 (p=0.002), 3.34 (0.8) points (22%) with DIZ102 (p<0.001) and 2.5 (0.8) points (16%) with LCIG (p=0.002). Despite the about 4 times higher carbidopa concentrations with DIZ101 and DIZ102 as compared to LCIG there were no differences in motor examination ratings with respect to UPDRS (Fig. 1A) or UDysRS (Fig. 1B) between DIZ101, DIZ102 and LCIG at any of the assessed time points 1.5h, 5h, 6h, 7h and 14h. TRS ratings produced the same result (not shown). Similarly, the unfiltered PKG bradykinesia (BK) and dyskinesia (DK) scores (Fig. 2AB) improved rapidly after treatment onset and did not differ between treatments in any of the predefined periods of infusion (0-2h, 2-8h, 8-16h)..

Conclusion

In 18 PD patients treated with DIZ101, DIZ102 and LCIG in a random crossover order, there was no observable trend for lower levodopa efficacy on motor symptoms, despite the previously reported higher carbidopa concentrations with DIZ101 and DIZ102 compared to LCIG. This indicates, in line with previous reports[2,3] that high blood levels (up to approximately 800 ng/mL) of carbidopa do not reduce the CNS effect of levodopa.

Take home message

Subcutaneous (DIZ102) and intravenous (DIZ101) levodopa/carbidopa infusion are as efficacious as LCIG regarding motor function in advanced PD, despite much higher carbidopa blood concentrations

References

1) Bergquist et al. Pharmacokinetics of Intravenously (DIZ101), Subcutaneously (DIZ102), and Intestinally (LCIG) Infused Levodopa in Advanced Parkinson Disease.Neurology 2022;99:e965-e976.
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3) Trenkwalder et al. Increased dose of carbidopa with levodopa and entacapone improves "off" time in a randomized trial. Neurology. 2019;92(13):e1487-e1496.