THE NMDAR ANTAGONIST DEXTROMETHADONE INCREASES PLASMA BDNF LEVELS IN HEALTHY VOLUNTEERS: A PHASE 1CLINICAL STUDY

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Introduction: Brain-derived neurotrophic factor (BDNF), a neurotrophin widely expressed in the central nervous system, plays an important function in neuronal plasticity. Recently, BDNF has been investigated as a biomarker of treatment response in depression and has been implicated in the mechanism of action of ketamine, an N-methyl-D-aspartic acid receptor (NMDAR) antagonist with rapid anti-depressant effects. Dextromethadone, the d-isomer of the dl-methadone racemic mixture widely used for the treatment of pain and addiction, is currently under investigation for the treatment of depression and is free from relevant opioid activity at doses exerting NMDAR antagonistic activity; in particular, dextromethadone is thought to exert low affinity blocking action on pathologically open NMDAR.

Methods: This study was conducted as part of a randomized, double-blind, placebo-controlled phase 1clinical trial of dextromethadone administered orally for 10 days at a dose of 25mg to healthy volunteers admitted for 14days to a Clinical Research Unit (CRU). Sampling for testing for BDNF plasma levels was performed before any treatment and 4hours after administration of dextromethadone 25mg (six patients) or placebo (two patients) on days 2, 6and 10. Plasma levels of BDNF were measured by means of an ELISA kit, following the manufacturer's instructions. Data are presented as mean ±SD. The statistical analyses were performed by means of GraphPad Prism and SPSS software. The Wilcoxon Signed Ranks test was performed to compare BDNF concentrations before any treatment and 4hours after administration of dextromethadone or placebo on days 2, 6and 10. We also checked a Spearman correlation between plasma dextromethadone and BDNF concentrations.

Results: In the d-methadone treatment group, 6of 6subjects (100%) showed an increase in BDNF levels post dextromethadone treatment compared to BDNF pre-treatment levels (d-methadone group: mean (±SD) = 0.84ng/ml (0.60); placebo group: mean (±SD) = 0.81ng/ml (0.38)) with post-treatment day 10 (last day of treatment) BDNF plasma levels ranging from twice to 17times the pre-treatment BDNF levels (d-methadone group: mean (±SD) = 5.84ng/ml (2.83); placebo group: mean (±SD) = 0.79ng/ml (0.30)) ($p=0.028$at day 2, $p=0.043$at day 6, and $p=0.028$at day 10, all vs BDNF plasma levels before treatment); the smallest increase on day 10 (twice the pre-treatment level) was seen in the study subject with the smallest day 10 dextromethadone level, Cmax and AUC and the longest Tmax among all 6treated subjects, consistent with a lower d-methadone pharmacokinetic disposition with respect to other treated subjects. By contrast, in the two placebo subjects, where as expected dextromethadone levels were 0, the BDNF plasma levels remained unchanged. Plasma BDNF levels measured at day 2and day 10 were significantly correlated to the plasma levels of dextromethadone when placebo subjects are included in the analysis. At the tested dose of 25mg per day for ten days dextromethadone did not cause psychotomimetic or opioid side effects. No signs of withdrawal upon abrupt discontinuation of dextromethadone could be observed.

Conclusion: The administration of 25mg of dextromethadone significantly increases BDNF plasma levels in healthy subjects compared to placebo; the increase started at least on day 2and persisted throughout day 10. Despite the study limitations, its findings add evidence consistent with the results of preclinical studies demonstrating that d-methadone exerts an antidepressant-like activity in animal models of depressed behavior comparable to that of ketamine. Considering the overall acceptable tolerability and safety profile of d-methadone emerged from two Phase 1studies, d-methadone has the potential to be a safer and less burdensome treatment alternative to ketamine. An undergoing Phase 2a study is currently assessing the tolerability, safety and antidepressant efficacy in patients with depression.