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Intra-nasal Esketamine Induced Psychotic Disorder in a Post Covid-19 Major Depressive Episode: a case report.

Trouble psychotique induit par l'Esketamine intra-nasale dans un épisode dépressif majeur post-Covid-19 : un cas clinique

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Mots-clés : Esketamine ; idées suicidaires ; troubles dépressifs majeurs ; psychoses ; induites par une substance ; COVID-19 ; neuropsychiatrie

Intranasal esketamine (IN-ESK) can treat severe major depressive episodes (MDE) with suicidality (1). While MDE are frequent after COVID-19 (2), the safety of IN-ESK after COVID-19 infection is unknown. To our knowledge, no psychotic episode induced by IN-ESK is reported, albeit ketamine abusers have higher rates of psychosis (3,4).

Mrs. A is a 64-year old woman, without any history of mental disorder, and an history of stabilized high blood pressure treated with ramipril (5mg/d).

She had a COVID-19 acute infection in April 2020, with a lingering anosmia, suggesting alterations of the olfactive epithelium caused by Sars-CoV-2 (5).

Four months later, Mrs A was hospitalized for a severe MDE with stupor, guilt feelings and suicidal thoughts (HDRS-21 score: 40). After non-response to venlafaxine (225 mg/d, venlafaxinemia: 700 ng/mL, therapeutic

range [70-250]) and mirtazapine (30 mg/d) for 6 weeks with optimal clinical tolerance despite venlafaxine overdose, treatment was switched to vortioxetine (10 mg/d).

One week after, considering the MDE's severity, suicidal thoughts and the unavailability of electroconvulsivotherapy due to limitations in the COVID-19 pandemic context, Mrs. A was treated with IN-ESK (58mg/session). After the first session, the patient presented unusual visual and olfactive hallucinations, associated with psychomotor agitation. Those symptoms disappeared in 24 hours. During the second session 4 days later, we noticed visual hallucinations associated with anxiety, disorganization, and delusions with interpretative and intuitive mechanisms. The BPRS at that time scored 66/126 (for a 55/126 cut-off). Thus, IN-ESK and vortioxetine were stopped and chlorpromazine (100 mg/d) was started . Delusion disappeared after 8 days, with a significant decrease on the BPRS (score 44/126) and hallucinations after 20 days; the MDE symptoms decreased 12 days after esketamine treatment (HDRS- 21 score: 17).

Blood examinations (i.e., blood formula, renal and hepatic function assessment, plasmatic C-reactive protein, calcemia, thyroid hormones) were normal. The EEG, which showed rapid desynchronizing rhythms compatible with an encephalopathy on day 4, returned to baseline after one month. The brain MRI showed a Fazekas I leukopathy and the neuropsychological assessment was normal. The pharmacogenetic analysis evidenced a mutation associated with a poor metabolizer CYP2B6 profile (c.516G>T) (6). Because no argument supported the hypothesis of an infectious or autoimmune encephalopathy, no lumbar puncture was performed.

The patient left the hospital after 28 days, treated by vortioxetine 15mg/day, diazepam 10mg/day and chlorpromazine 100mg/day. The residual symptoms at discharge were mainly anxiety and a psychomotor slowing. A consultation 4 month after the episode found a complete remission (HDRS-21 score : 6), and no psychotic symptom.

We suggest that IN-ESK induced a psychotic episode in a patient with a post COVID-19 MDE. We propose three causes for this severe side effect. First, due to persistent alterations of the olfactive epithelium caused by Sars-CoV-2, IN-ESK may have cross the olfactive epithelium and access the cerebrospinal fluid through an undetected meningeal breach. Second, the CYP2B6 poor metabolization may have favored an overdose of IN-ESK (7) inducing a psychotic episode. Third, because IN-ESK and vortioxetine are partially metabolized by the CYP3A4, an interaction between those two molecules resulting in an overdose of IN-ESK can not be excluded.

IN-ESK should be used with caution in post COVID-19 MDE, especially if anosmia is present. Moreover, pharmacogenetic investigations of CYP2B6 may be recommended in patients treated with IN-ESK.

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