Dorsal Prefrontal Cortex Impairment in Methoxetamine-Induced Psychosis: an ^{18}F-FDG PET/CT Case Study

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Methoxetamine [2-(3-methoxyphenyl)-2-(ethylamino) cyclohexanone, MXE] is a arylcyclohexylamine derivative of ketamine (KET), which differs from the latter for the insertion, on the phenyl ring, of 3-methoxy and N-ethylamino groups in place of 2-chloro and N-methylamino groups respectively. The N-ethylamino group accounts for MXE increased potency and duration of action as compared to KET, whereas the 3-methoxy group is responsible for decreased analgesic and anesthetic properties. MXE is available in form of white powder, and it is assumed under different routes of administration, including nasal insufflations, oral consumption, sublingual or rectal administration, intramuscular (IM) or intravenous (IV) injections.

Dosages can range from 20 to 100 mg for oral administration and from 10 up to 100 mg for IV and IM administrations. MXE mechanism of action and effects are believed to be mediated through a combination of N-methyl-D aspartate (NMDA) receptor antagonism, dopamine reuptake inhibition, and muscarinic cholinergic and serotonin (5-HT2) receptors agonism. Human cytochrome CYP2B6 and CYP3A4 are believed to be involved in initial metabolic pathway, which ultimately leads to N-desethyl(nor)methoxetamine, MXE main biologically active metabolite.

According to consumers' self-reported experiences, effects of MXE are similar to those of KET, except for longer duration and longer delay onset, which may lead to an increased risk of re-dose. MXE desired psychotropic effects include euphoria, increased empathy and social interactions, pleasant intensification of sensory experiences, dissociative experiences from physical body (i.e., M-Hole). At higher doses MXE can be responsible for particularly unpleasant effects such as near-death experiences or marked alterations in consciousness, including catatonia, hallucinations, confusion, agitation, delirium, shift in perception of time and space. MXE intoxication may also cause neurological symptoms such as cerebral ataxia, dysarthria, nystagmus, and motor incoordination. In addition, MXE may induce sympathomimetic toxicity as evidenced by tachycardia and hypertension [1].

Recent studies and reports confirmed MXE abuse liability as well as the risk of fatal intoxication when MXE is assumed at high doses or in combination with other substances [2]. Along with other novel psychoactive substances (NPSs), MXE has been recently classified as a scheduled I substance in the European Union and in other countries. Evidence supports the "psychotomimetic" properties of MXE which, possibly via NMDA receptor modulation, may elicit psychotic phenomena (e.g., alterations in perception, thinking, and feeling), as well as neurocognitive dysfunction [3].

Case Report

We report the case of a 23-year-old man, whose child development was apparently normal and his family history free from psychiatric disorders. He reported occasional consume of alcohol, cannabis, ketamine, and LSD during late adolescence. However, his past medical history was free from any major psychiatric disorder. One day his mother found him unconscious in his room. He was immediately brought to the Emergency Department (ED) where physical examination and laboratory analysis revealed a state of acute kidney (serum creatinine: 2.34 mg/dL; serum cystatin C: 1.42 mg/dL; Urea: 55.8 mg/dL; CPK 17.000 U/L) and respiratory failure (arterial PaO_2: 52 mmHg; arterial $PaCO_2$: 50 mmHg). ECG also showed an incomplete right bundle branch block. Blood and urine samples were negative for ethanol, benzodiazepines, cannabinoids, cocaine, amphetamine, methadone, opioids, and tricyclic substances. He was firstly managed with supportive care, including tracheal intubation and mechanical ventilation. Symptoms resolved after two weeks of treatment with atenolol 100 mg/d, clonidine 150 mg/d, nitrosorbide 40 mg/d, and hemodialysis. A 10 mL serum (kept at – 20° C) sample collected at the ED was sent to the Pavia Poison Control Center which used gas chromatography-mass and liquid chromatography-tandem mass spectrometry techniques to identify possible NPs. MXE traces were confirmed within patient's blood serum at a dosage of 0.29 μg/ml. Once patient's medical conditions restored, he was transferred to a psychiatric residential treatment center. Here, he sufficiently dealt with daily activities and slightly conversed with other patients or staff members. A blunted affective responsiveness, including curbing of interests, diminished social drive and impoverished speech was noticed, without marked abnormalities of mental state or behavior. He also reported to continuously experience visual and auditory hallucinations as if during MXE "high". He admitted to having IV injected himself an unspecified amount of MXE retrieved on internet, after his girlfriend revealed him she wanted to break up. He was administered a psychometric assessment, which indicated severe dissociative symptoms, including detachment from reality and absorption in imaginative thoughts, along with marked affective withdrawal and motivational anhedonia. The patient also underwent a neuropsychological evaluation, which revealed a mild impairment of verbal fluency, working memory and increased distractibility (**Table 1**). Clinical electroencephalography was normal. He was prescribed a magnetic resonance imaging (MRI) and a [18F]-fluorodeoxyglucose-Positron Emission Tomography integrated with computed tomography (^{18}F-FDG PET/CT). Axial/sagittal T1-weigthed, axial FLAIR, and axial/coronal T2-weighted MRI images revealed no morphological or structural alterations within brain tissues and the whole ventricular system.

Brain FDG distribution analysis of the PET/CT was performed by using the Scenium software (Siemens) which allows to compare FDG uptake of a single subject with a standardized database of

normal subjects. The scan showed a bilateral deficit of tracer uptake within Middle frontal gyrus (MFG), more evident in the right side (**Figure 1**). This was confirmed with the software analysis by a significant difference of the number of standard deviations (SDs) between the mean standardized uptake value (SUV) of the patient compared to normal subjects (-3.5 SD in the right side and -2.5 SD in the left side).

He was then prescribed aripiprazole 15 mg/d and N-acetylcysteine 2 g/d given the efficacy of the compounds in treating psychotic symptoms and substance-related withdrawal, partially via glutamate neurotransmission restoring [4-5]. Symptoms gradually improved within twelve weeks (**Table 1**). He was finally discharged with a DSM-5 diagnosis of Substance-Induced Psychotic Disorder.

MXE mechanisms of neural toxicity have not yet been established in humans. Similar to other NMDA antagonists, MXE proved to affect emotional processing and working memory in rodent models possibly via increased phosphorylation of ribosomal proteins [6-7]. The present case-report documented a bilateral middle frontal gyrus (MFG) impairment, as revealed by ^{18}F-FDG PET images, in MXE-induced psychotic disorder. The glutamate hypothesis suggests that hypofunction of NMDA receptors may account for the pathophysiology of psychotic disorders, given that NMDA antagonists mimic both positive and negative symptoms of disease as well as cognitive impairments. Along with other lateral prefrontal and parietal bilateral areas, MFG, of which dorsolateral prefrontal cortex (DLPFC) is part, constitute a central executive network (CEN), whose activity is critical to goal-oriented cognitive functions, including working memory and sustained attention. A decreased local resting state activity within CEN structures (e.g., DLPFC), has been supposed to mediate, in several psychiatric disorders, a shift from external, goal-oriented mental contents, to internal, self-directed thoughts. Such an imbalance between internal and external mental contents in awareness, may ultimately leads to several psychopathological symptoms, including rumination, social withdrawal and lack of motivation [8]. Moreover, lower metabolic rates in DLPFC, as revealed by PET studies, have been implicated in the pathophysiology of several clinical features among psychotic subjects, including negative symptomatology and impaired cognitive functioning [9]. MXE may thus share psychotomimetic properties of KET and other NMDA antagonists, which, partially through MFG impairment, may induce symptoms such as perceptual aberrations, working memory impairment, and emotional withdrawal that resemble early stages of schizophrenia [10].

NPSs acute intoxication has currently become a public health major concern, because of relatively easy accessibility to these compounds and difficulty in identifying them with routine laboratory techniques. Similarly, clinical features of NPSs intoxication are difficult to recognize and classify. This report highlights that MXE intoxication may produce severe brain damages even after a single

consumption. Therefore, patients should be carefully warned of the serious risks they incur when assuming NPSs.

Disclosure

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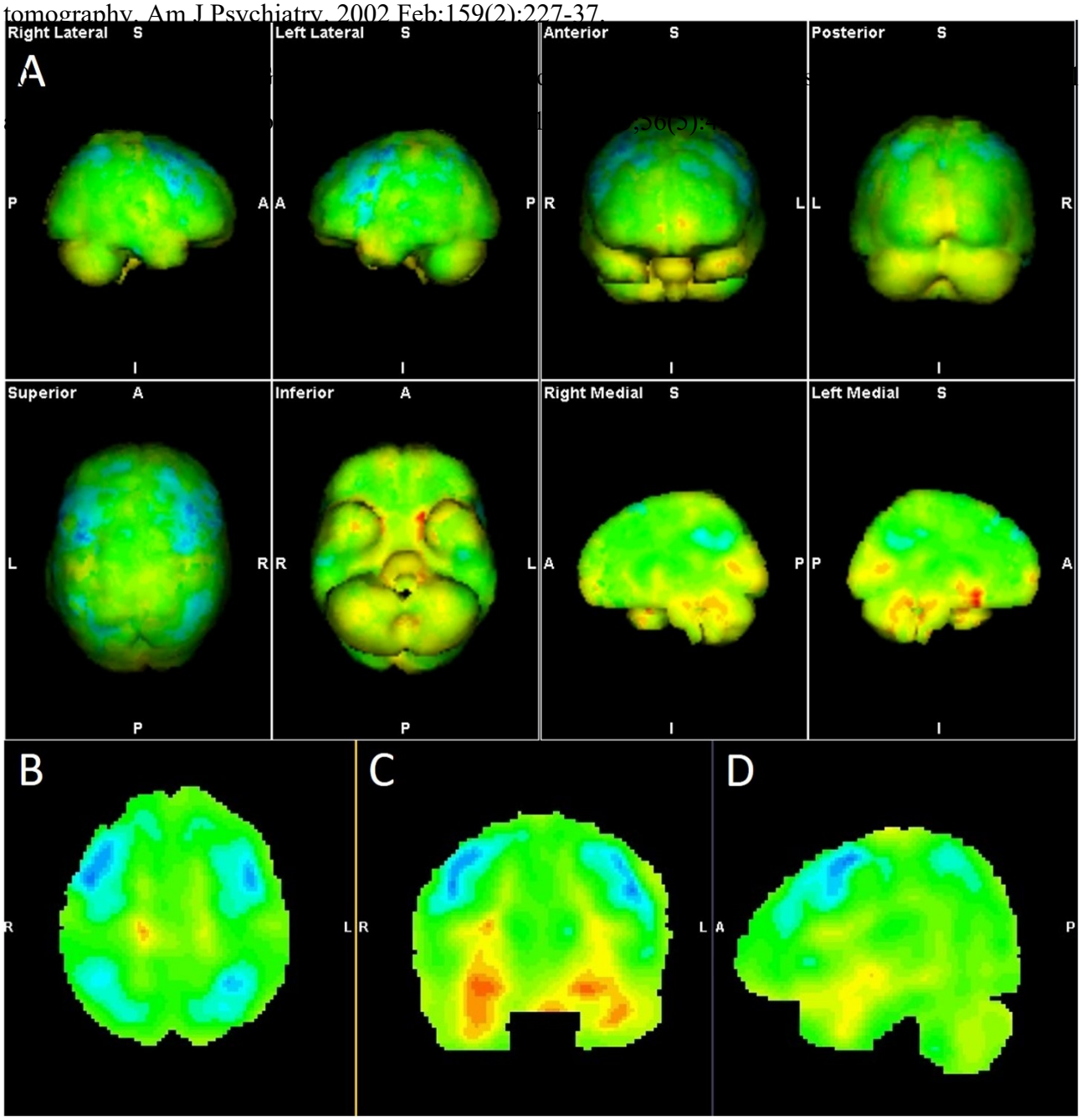

Figure 1. Brain ^{18}F-FDG PET/CT. **A** (series): multiple views of global FDG uptake parameterized with mean SUV difference from normal subject (Scenium analysis). **B**, **C**, **D**: respectively axial, coronal and sagittal view of PET scan where a bilateral lower FDG uptake is evident in MFG

ASSESSMENT	PATIENT SCORE	
	ADMISSION	DISCHARGE

PANSS		
Positive Symptoms	*12*	*7*
Negative Symptoms	*30*	*20*
General Psychopathology	*32*	*21*
Total	*74*	*48*
BNSS		
Anhedonia	*13*	*8*
Distress	*3*	*2*
Asociality	*7*	*5*
Avolition	*7*	*5*
Blunted Affect	*11*	*9*
Quantity of Speech	*7*	*6*
Total	*48*	*35*
TEPS		
Anticipatory Pleasure	*21*	*17*
Consummatory Pleasure	*26*	*23*
Total	*47*	*40*
DES-II		
Amnesia	*10*	*6*
Depersonalization-Derealization	*41.6*	*17.14*
Absorption	*35*	*13.64*
Total	*22.15*	*11.79*
MMSE	*28*	*29*
TMT A		
Time	*51*	*35*
Errors	*1*	*0*
TMT B		
Time	*124*	*92*
Errors	*0*	*0*
DIGIT SPAN		
Forward	*3*	*5*
Backward	*4*	*6*
Total	*7*	*11*
PVF	*32*	*51*

Legend: BNSS, Brief Negative Symptoms Scale; DES-II, Dissociative Experience Scale; MMSE, Mini Mental State Examination; PANSS, Positive and Negative Syndrome Scale; PVF, Phonemic Verbal Fluency; TEPS, Temporary Experience Pleasure Scale; TMT, Trail Making Test.

Table 1. Psychometric and neuropsychological evaluation.