Long-term ketamine self-injections in major depressive disorder: focus on tolerance in ketamine`s antidepressant response and the development of ketamine addiction

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Abstract

Presently, sub-anaesthetic ketamine is of special interest for depression research due to its rapid and potent but short-living antidepressant response (after-effect). The presented case is the first one in the literature which deals in detail with the transfer from ketamine`s antidepressant action to ketamine addiction. A 50-year-old anaesthetic nurse, who had never been treated with antidepressants before, started with self-injecting ketamine racemate 50 mg IM once a week to cope with her major depression. She continuously stole ketamine from hospital stocks. Due to a gradually developing tolerance in ketamine`s excellent antidepressant action she stepwise increased dose and frequency of ketamine self-injections finally to up to daily 2 g IM (3-fold her anaesthetic dose) in the following 6 months. This was accompanied by the development of ketamine addiction, loss of consciousness, dissociative immobility and amnesia. A following inpatient detoxification treatment was characterized by a strong craving for ketamine and, later on, by the occurrence of a severe depressive episode remitting on venlafaxine. A 14-week follow-up documented a normal condition without any ketamine sequelae, such as craving, psychosis, depression or cognitive abnormalities. To conclude, awareness to the development of ketamine addiction even in patients who received ketamine for antidepressant purposes is important.

Introduction

Ketamine is a derivate of phencyclidine (PCP) approved to start and maintain anaesthesia or analgesia. It is widely used in veterinary medicine or battlefield pain control and is characterized by manifold dose-dependent acute and delayed psychoactive actions in humans (Jansen 2000; Wolff & Winstock 2006; Morgan & Curran 2012; Marland et al. 2013). Anaesthesia is usually started with ketamine 1-2 mg/kg IV or ketamine 8-10 mg/kg IM (Table 1), which does not impair breath- and gag-reflexes and can produce vomiting and amnesia (Marland et al. 2013). Sub-anaesthetic doses are associated with analgesia, tachycardia, stimulation, visual hallucinations, psychedelic and dissociative (e.g. perception that the self is separated from the body) sensations, occurring quickly after injection and lasting 15 minutes up to an hour (Jansen 2000; Wolff & Winstock 2006; Morgan & Curran 2012). These acute sensations were coupled to pleasant (usually euphoria and relaxation) and sometimes unpleasant (e.g. panic, agitation) feelings (Jansen 2000; Wolff & Winstock 2006; Morgan & Curran 2012). Higher and frequent ketamine dosing is accompanied by stronger dissociations which dose-dependently can culminate in catatonic conditions or a “K-hole”, such as mystic visions, out-of-body-sensations, near-death- or rebirth-experiences (Jansen 2000; Wolff & Winstock 2006; Morgan & Curran 2012). Prolonged recreational use of ketamine, which is preferentially intranasal, can be complicated by transient delusional thinking and cognitive impairment (Jansen 2000; Wolff & Winstock 2006; Morgan & Curran 2012) as well as with ulcerative cystitis, hepatic dysfunction, impaired gallbladder activity, kidney dysfunction, gastritis, and colicky epigastric pain (“k-cramps” or “k-belly”) (Kalsi et al. 2011, Morgan & Curran 2012, Bokor & Anderson 2014). In their dissociative and psychotic states, recreational ketamine users were at special risk of injuries due to falls, burns, “date rape”, traffic accidents, jumping from heights, freezing or drowning (Jansen 2000; Kalsi et al. 2011). Ketamine use should be considered in the investigation of unexpected deaths of otherwise healthy people (Schifano et al. 2008). An increase in addictive ketamine use had prompted several countries, such as USA (1999), Hong Kong (2000), Taiwan (2003), Canada (2005), UK (2006) and India (2013), to regulate ketamine in its narcotic acts(Kalsi et al. 2011; Morgan & Curran 2012; Bokor & Anderson 2014). In Germany, however, ketamine is currently not regulated by law.

Presently, ketamine is of special interest for depression research because ketamine was found to provide a rapid and robust antidepressant action assumed to be primarily attributed to ketamine`s property to block glutamate NMDA-receptors non-competitively (Duman et al. 2012; Naughton et al. 2014). However, there are some more actions of ketamine, e.g. on hyperpolarization-activated cation channel 1 and aminergic, cholinergic and opioid systems, that should be mentioned (Mion & Villevieille 2013, Sleigh et al 2014).

An increasing number of studies demonstrated a rapid and robust antidepressant response occurring subsequent to sub-anaesthetic parenteral ketamine doses (usually a single ketamine infusion of 0.5 mg/kg over 40 minutes) in 50-80% of the cases when applied the first time to patients with treatment resistant depressive symptoms of major depressive disorder or bipolar disorder (Katalinic et al. 2013; Naughton et al. 2014; Fond et al. 2014). The antidepressant response emerged as an aftermath within the first hours after a single ketamine administration, peaked in the next 24 to 48 hours and dissipated within the following 3 to 7 days (Katalinic et al. 2013; Naughton et al. 2014; Fond et al. 2014). A similar beneficial ketamine-response was found in the treatment of obsessive compulsive disorder (Rodriguez et al. 2013). Because ketamine`s antidepressant response was only transient the effects of repeated and more frequent ketamine administrations to treatment resistant depressives were and are under study (Murrough et al 2013; Rasmussen et al 2013; Naughton et al 2014; Fond et al 2014; Shiroma et al 2014). On the other hand, depressive states were reported in frequent recreational ketamine users, both in current and ex-users (Jansen & Darracot-Cankovic 2001; Morgan & Curran 2012; Tang et al 2013). The following case report addresses this area of conflict and describes in detail the course of a patient suffering from both major depressive disorder and dependence on ketamine. It is assumed that frequent, finally addictive ketamine self-injections of the patient were attributed to a preceding development of tolerance in ketamine`s antidepressant response. To date, there is only scant evidence of a tolerance in ketamine`s antidepressant response (Liebrenz et al. 2009; Cusin et al. 2012; Chilukuri et al. 2013). Ketamine detoxification treatment was complicated by an intense craving for ketamine and the development of a severe depressive episode as reported hereinafter. .

Table 1: Route of administration, bioavailability, and the therapeutic starting dose of ketamine racemate*

Route of administration	Bioavailability	Starting dose (adults)
intravenous (IV)	100%	anaesthetic dose: 1-2 mg/kg bolus analgesic/sedation dose: 0.25-1 mg/kg bolus antidepressant dose: 0.1-0.5 mg/kg over 40-45 minutes (Berman et al. 2000, Zarate et al. 2006, Zarate et al. 2012, Lai et al. 2014) antisuicidal dose: 0.2mg/kg over 1-2 min (Larkin & Beautrais 2011) or 0.5 mg/kg over 40 minutes (Thakurta et al. 2012, Zarate et al. 2012, Price et al. 2014)
Intraosseous (IO)	100%	anaesthetic dose: 1-2 mg/kg analgesic/sedation dose: 0.5-1 mg/kg antidepressant dose: n.a. antisuicidal dose: n.a.
Intramuscular (IM)	93%	anaesthetic dose: 8-10 mg/kg analgesic/sedation dose: 4-5 mg/kg antidepressant dose: 0.25-1mg/kg (Glue et al. 2011, Harihar et al. 2013, Chilukuri et al. 2014) antisuicidal dose: n.a.
Oral	16-20%	anaesthetic dose: n.a. analgesic/sedation dose: 500 mg maximum antidepressant dose: 0.5 mg/kg (Irwin et al. 2013) antisuicidal dose: n.a.
Intranasal (IN)	45-50%	anaesthetic dose: 3-9 mg/kg analgesic/sedation dose: 0.25-4 mg/kg antidepressant dose: 50 mg (Lapidus et al. 2014) antisuicidal dose: n.a.
Rectal	25-30%	anaesthetic dose: 8-15 mg/kg analgesic/sedation dose: 50 mg antidepressant dose: n.a. antisuicidal dose: n.a.

*anaesthetic as well as analgesic/sedation doses were taken from the review of Marland et al. (2013). Not included is the sublingual route (bioavailability~30%) being described to be also associated with an antidepressant response using 10 mg from a 100 mg/ml ketamine solution for 5 min and swallowed (Lara et al. 2013).n.a.=not applicable

Case presentation

Outpatient consultation

Mrs. K, a 50-year-old nurse anaesthetist (71 kg, 168 cm), introduced herself being supported to quit using ketamine she would be hooked on for 3 to 4 months. Her

psychiatric history revealed a major depressive disorder, which had never been treated professionally before. There were no hints at a bipolar disorder. Her first depressive episode had developed postpartum when she was 28 years old, was mild to moderate and lasted about 4 months. One or two bottles of wine, distributed across the week, had helped her to cope with anhedonia, sleeplessness, restlessness and lack of energy. Initially, her relief had persisted over several days after drinking 2 or 3 glasses of wine. Rarely, she had taken up to 20 mg diazepam a week to overcome pronounced restlessness and sleeplessness. She could easily stop her regular alcohol and irregular benzodiazepine use when the depressive episode had been remitted spontaneously. She had learnt this strategy from her mother, who occasionally had been depressive but not addicted because she apparently was able to abstain in her periods without depression, just like Mrs. K. herself.

The second depressive episode developed a year ago, when her beloved sister, who had suffered also from depression, unexpectedly died. Again she tried to self-treat her depression with a few glasses of wine being finally used nearly daily. After four weeks she recognized that wine did not help again and therefore, she stopped drinking without any noticeable alcohol withdrawal symptoms. However, acute nonspecific back pain developed, which urged her to consult a pain specialist. After having no benefit from a combination of non-steroidal anti-inflammatory drugs and tramadol she was injected by her physician with a single dose of ketamine 25 mg IM, which immediately improved her pain and also her depression for a week. When pain and depression returned she started to self-inject ketamine, which she stole from the hospital stocks. Initially, she injected ketamine 50 mg IM to herself once a week. Soon after injection she felt pleasant for approximately 20 minutes. Euphoria and relaxation was accompanied by psychedelic experiences (sensation of inner peace, visual hallucinations, calmness, feeling light and serenely with deep empathy), mild palpitations and pain relief. Thereafter, relief of depression arose that persisted 5 to 8 days. In the course of 6-8 weekly injections pleasant and psychedelic feelings did not recur and the sought antidepressant response to ketamine had decreased to merely 1 or 2 days. To counteract, Mrs. K. had increased dosage and frequency of ketamine injections within the next 4-6 weeks to up one daily injection of 0.4 g IM (5.6 mg/kg; 60% of her anaesthetic dose). Regardless, pleasant feelings recurred only for a few minutes and the sought antidepressant response to ketamine vanished during the

next day promoting daily self-injections. Her depression had been kept suppressed about 3 months with daily ketamine 0.4 g IM. She did not remember to have ever lost consciousness and excluded a wanting of acute pleasant feelings because those never came back after a few ketamine injections with this dose.

An increasing risk of being caught while stealing ketamine and an arising of dose-dependent discomfort under ketamine, such as going through unpleasant dissociation (panic because she perceived that she was unable to control her movements for several minutes), feeling of emptiness and subjective cognitive decline (loss of concentration, difficulty with word finding and impaired recall) prompted her to stop ketamine use several times. She had relapsed with ketamine each time within two or three days after ketamine cessation due to the emergence of a compelling urge for ketamine and restlessness. She was advised to take advantage of an inpatient detoxification treatment.

Inpatient treatments

Mrs. K. was admitted a week later. She reported to have continued the daily self-injections with ketamine 0.4 g IM. Outside her depression and alongside her whole “ketamine-experience” she had never needed to use alcohol or benzodiazepines. Moreover, she reported never using other drugs. The last ketamine IM injection would have been approximately 14 hours ago. She told being in an intended non-depressed condition without any dissociative or psychedelic sensations. Physical and psychiatric examination was unremarkable with the exception of a mild fibrosis of the right anterior thigh as well as poor concentration and slow thinking. Urine drug screen was positive for PCP) and negative for other drugs including benzodiazepines. Because she denied ever have taken PCP we assumed cross-reactivity between ketamine and PCP in the used immunoassay urine drug test (Shannon 1998). A gas chromatography/mass spectrometry, which can distinguish between ketamine and PCP, was not performed. Routine lab tests, carbohydrate deficient transferrin, electrocardiography, electroencephalography, cranial MRI and abdominal ultrasound were unremarkable. There was no hematuria, abdominal pain or urinary tract symptoms (Kalsi et al. 2011). Mini-Mental-Status-Test (Folstein et al. 1975) and Montreal Cognitive Assessment (MoCA) (Nasreddine 2015) were normal as well as Hamilton-Depression-Score (Hamilton 1960; HAMD 2015) (6 points, Figure 1). Soon after ketamine cessation she described an increasing desire for ketamine which was

accompanied by restlessness. She did not want to be medicated. Further withdrawal symptoms did not occur. After 3 days the treatment was terminated prematurely by Mrs. K. She negated her plan to return to work.

Twentyfive days later she was taken from work directly to detoxification ward because she was found to be confused and euphoric with fourteen ketamine vials (50mg/ml and 100mg/ml) and syringes from the hospital stocks in her pockets and purse. She conceded to have injected up to ketamine 2 g IM per day, subdivided into several sittings, to satisfy her intense urge for ketamine being also the reason why she had quitted the recent detoxification treatment. When her husband was informed about Mrs. K`s re-admission he reported that Mrs. K. had several incidents of unconsciousness, memory loss or confusion in the last two weeks. Therefore, he had called for an ambulance four times. At its arrival, however, Mrs. K. being always completely recovered was not able to remember what had happened before. Also “K-holes” could not be remembered by Mrs. K.

Physical and psychiatric examinations were not different from the first investigation one month ago. MoCA, however, revealed an impairment of executive function, attention and delayed recall, which was vanished in re-examination on day 7 of this second detoxification treatment. HAMD-score was normal one day after admission (7 points) and climbed up to 27 points within the next 7 days (Figure 1). At that time, Mrs. K. reported feeling deep sadness, loss of pleasure and appetite, difficulty concentrating, inner tension, lower back pain and loss of energy, which turned somewhat better over the day and was accompanied by disturbed sleep. She objectively had symptoms of a severe depressive episode (Cooper & WHO 1994; APA 2014). Again, she did not want any medication and insisted on premature dismissal (Figure 1).

Two weeks later she was brought to admission by her husband in an alcohol-intoxicated and confused condition (BAC 0.22%, urine drug screen negative). When she was sober she reported an overwhelming urge for ketamine that had forced her to discontinue the recent inpatient treatment. This urge had developed in the first 36 hours of ketamine abstinence and preceded her depressive state. She had learnt to cope with her depression rapidly when using ketamine. Coming home, however, she had realized being dismissed by her employer, thus having no further access to ketamine. In her need she had started to drink vodka. A daily use of up to a third of a bottle of vodka or about three quarters of a bottle of wine would indeed have

produced some relief of her ketamine craving and depression. She quickly had to drink more to keep the relief. Finally, she drank daily one bottle of vodka resulting in a complete disorganization and several falls during the intoxications. One day after admission, HAMD-score was 12despite the development of moderate alcohol-withdrawal syndrome, requiring clomethiazole (Morgan 1995) in the first 4 days of the treatment. In the following, her depressive symptoms returned and HAMD-score increased gradually to 32 points at the end of the third week of the detoxification treatment (Figure 1). This was accompanied by a moderate tension headache and, again lower back pain. At this time, the patient agreed with an evidence-based antidepressant treatment. In the next 3 weeks her depression responded tovenlafaxine (de Silva et al 2012) (Figure 1). Simultaneously, her pain dissipated. She was transferred to a 3 month inpatient rehab facility. Afterwards, she was treated as an outpatient in our ward. Her depression was meanwhile remitted (Figure 1) and she reported on no further necessity to use ketamine, alcohol or benzodiazepines. Ability to concentrate had normalized and MoCA did not reveal cognitive abnormality. She was proud of having found a new job, at present in the ambulatory care without any access to ketamine or other narcotics. Random drug urine tests including a screening for benzodiazepines, ethyl glucuronide and phencyclidine were all unremarkable.

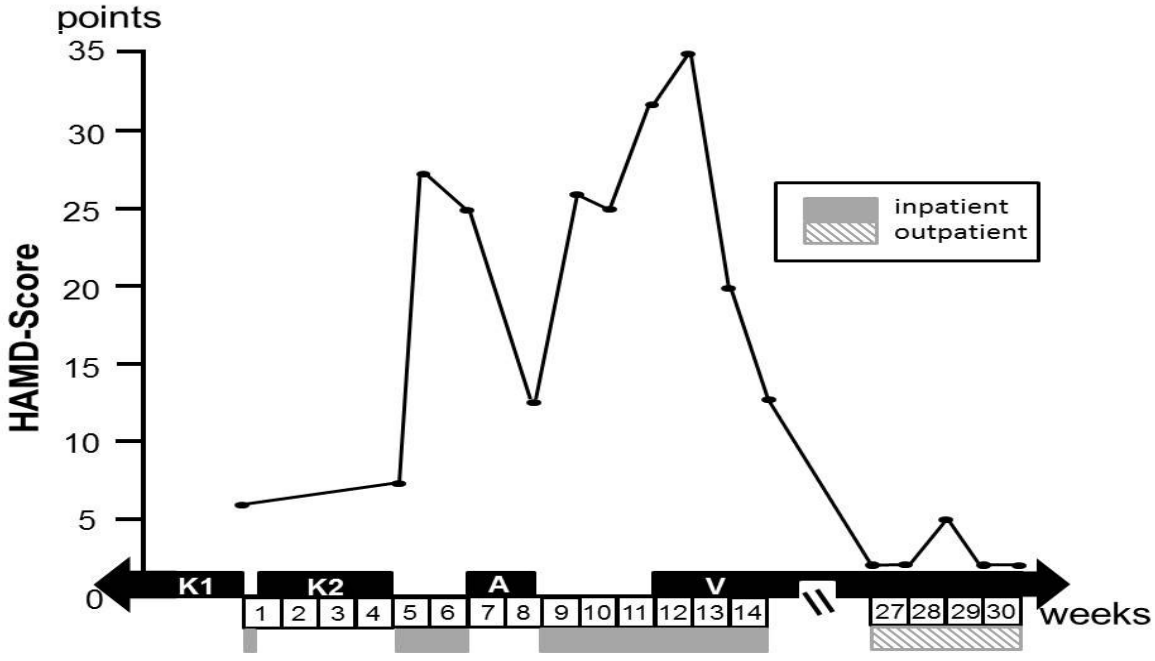

Figure 1: Occurrence of a severe depressive episode during ketamine detoxification and its response to venlafaxine. Abbreviations: K1=ketamine racemate in the range

of 0.4 g/day IM., K2=ketamine racemate up to 2g/day IM, A=alcohol, V=Venlafaxine hydrochloride extended-release (up to 225 mg/day), gap=3 months inpatient rehab treatment, HAMD=Hamilton Depression Scale$_{21\text{-item}}$ (ratings were based on items 1-17 according to Hamilton (Hamilton et al. 1960; HAMD 2015): ≤7 points = remission, 8-13 points: mild depression, 14-18 points: moderate depression, ≥19 points: severe depression).

Discussion

This case report may add the following information. First, daily ketamine doses in the range of 0.4 g (5.6 mg/kg) IM about 3 months seem to be potently antidepressant, albeit poorly tolerated over time due to development of addiction, dissociations and cognitive impairment. Second, depression relapsed swiftly, even after discontinuation of long-term and almost daily ketamine injections. Third, to provide further evidence of the occurrence of tolerance in ketamine`s antidepressant response. Fourth, frequent and uncontrolled self-injections of ketamine are addictive, even in patients with major depressive disorder. Fifth, ketamine addiction and withdrawal is dominated by an intense craving, even in patients with major depressive disorder. Sixth, to speculate for the first time on a putative antidepressant aftermath of alcohol ingestion if low and cautiously dosed (with respect to Mrs. K.`s self-treatment of her first depressive episode)

Relationship between major depressive disorder and ketamine addiction

The diagnosis of a “severe major depressive disorder” (DSM-5, 296.23) (APA 2014) or “recurrent depressive disorder, current episode severe without psychotic symptoms” (ICD-10, F33.2) (Cooper & WHO 1994) is supported by i) a prior depressive episode in the history of Mrs. K., ii) a positive family history for depression, iii) at least 7 depressive key symptoms observed over 6 weeks (Cooper & WHO 1994; APA 2014), and iv) her positive response to venlafaxine. However, there were no objective clinical data available prior to the Mrs. K.`s first clinical presentation when she was using ketamine 0.4g/day IM. Therefore, some uncertainty remains what her real clinical baseline was prior to the first detoxification.

The “addiction” diagnosis is supported by recurrent ketamine use and the development of withdrawal syndrome (craving and restlessness), tolerance in

pleasant feelings (euphoria, relaxation), continued ketamine injections despite having negative social consequences (stealing ketamine, threat of dismissal), harmful use (cognitive impairment, feeling of emptiness and loss of consciousness) and loss of controlling ketamine taking behavior. Thereby, at least 5 out of 6 ICD-10 criteria for "dependence on hallucinogens" (ICD-10, F16.20) (Cooper & WHO 1994) and at least 8 out 10 criteria for "severe other hallucinogenic use disorder" (DSM-5, 304.50) (APA 2014) were fulfilled. Ketamine cessation was directly followed by ketamine craving and then by waxing depressive symptoms indicating two different neurobiological conditions. However, it cannot be completely excluded that the depression (Figure 1) resulted from an outlasting and unsatisfied ketamine craving (c.f. diagnostic criterion C of major depressive disorder according to DSM-5 (APA 2015), or diagnostic criterion G3 according to ICD-10 (Cooper & WHO 1994). If ketamine would have caused her (then "secondary") depression, substance craving or substance relapse should be expected alongside the remission of her depression. There was no evidence for neither a ketamine craving nor a ketamine relapse up to date supporting the assumption that Mrs. K had used ketamine primarily to self-medicate her (then "primary") depression, just as recently hypothesized for depressive ketamine users (Morgan & Curran 2012). Although rather unlikely in this case, the depressive episode might have occurred independently from ketamine detoxification considering addiction to be a risk factor for depression in general (Boden & Fergusson 2011).

Return of a major depressive episode after ketamine cessation – durability of ketamine`s antidepressant action

The antidepressant response of single sub-anaesthetic ketamine injections (Table 1) normally lasted up to one week in treatment resistant depressives (Katalinic et al. 2013; Naughton et al. 2014; Fond et al. 2014). Repeated or serial sub-anaesthetic ketamine infusions (usually 0.5 mg/kg over 40 to 100 min, up to thrice weekly over 2 weeks) seemed to prolong the duration of ketamine`s antidepressant response; but depression relapsed (Nierenberg & DeCecco 2001) within 4 weeks after stopping ketamine in the vast majority of the treatments (Murrough et al 2013; Rasmussen et al. 2013; Shiroma et al. 2014). This promotes speculations about more sustained antidepressant responses, or even a stable remission following a longer period of more frequent and, if tolerable, even higher dosed ketamine injections. The present case discourages such speculations somewhat as it describes first evidence that a

continuous antidepressant response to daily ketamine injections (dosed 5 to 17 times higher than usual, Table 1) about several months can be followed by a swift return of a depressive episode after stopping ketamine.

Tolerance in ketamine`s antidepressant action *and ketamine addiction*

Rapid tolerance in ketamine`s characteristic acute psychoactive effects (euphoria, stimulation, analgesia, dissociative and psychedelic sensations) is well recognized and considered to be involved in the development of addictive behavior in recreational ketamine users (Jansen & Darracot-Cankovic 2001; Wolff & Winstock 2006; Kalsi et al. 2011; Morgan & Curran 2012; Boker & Anderson 2014). The trials on repeated or serial ketamine-infusions did not describe any tolerance in ketamine`s antidepressant response (Murrough et al. 2013; Rasmussen et al. 2013; Shiroma et al. 2014). However, these studies used i) intervals of 2 to 3 days between the infusions, which might be too long to induce tolerance in ketamine`s antidepressant response and ii) treatment durations of 2 weeks, which might be too short to induce tolerance in ketamine`s antidepressant response. In a recent case series, 3 treatment resistant depressives were exposed to sub-anaesthetic ketamine infusions according to an as needed design over 12 months (Szymkowicz et al. 2013). If looking on the results (Szymkowicz et al. 2013) one might speculate on some tolerance in ketamine`s antidepressant actions being embedded into highly intra- and interindividual ketamine responses. Further support for the existence of a tolerance in ketamine`s antidepressant response comes from a previous case report on a 55-year-old male depressive patient with co-occurring alcohol- and benzodiazepine dependence, who was described having a strikingly weakened antidepressant response to the second ketamine infusion if compared with the ketamine`s antidepressant response to the first infusion administered 35 days before (Liebrenz et al. 2009). Another patient with major depression had a faded antidepressant response to the second ketamine injection three days after the first one (Chilukuri et al. 2013). A female patient with bipolar depression had a recurrence (Nierenberg & DeCecco 2001) at 6 months receiving ketamine 50 mg IM every fourth day (Cusin et al. 2012). An adult female with a major depression being resistant to electroconvulsive therapy initially responded to ketamine infusions while on antidepressants and augmentation strategies, but this beneficial effect decreased along with more than 40 ketamine infusions given two times a week at least (Blier et

al. 2012). The present case report addresses tolerance in ketamine`s antidepressant response the clearest, although not directly observed. Nevertheless, Mrs. K had several features which might have facilitated the development of tolerance in ketamine`s antidepressant response; notably she i) had never been treated with antidepressants before, ii) self-injected ketamine daily about 3 months, iii) became addicted to ketamine, and iv) had an alcohol- and benzodiazepine use in her history, just as the 55-year-old male reported by Liebrenz et al. (Liebrenz et al. 2009).

Pharmacologically, tolerance in ketamine`s psychoactive effects might be explained by an extensive ketamine auto-induction of its metabolism (Kalsi et al. 2011) and by adaptions at least in dopaminergic and glutamatergic relays of various CNS-pathways, such as the cortico-striato-thalamic (mediating analgesia, psychosis, dissociation, anaesthesia) and the cortico-limbic circuits (mediating addiction, depression, analgesia) (Vollenweider & Geyer 2001; Rose et al. 2006; Persson 2013; Quintero 2013). There is strong evidence that acute ketamine is associated with a hyperdopaminergic and hyperglutamatergic state in parts of these networks (Wollff & Winstock 2006; Duman et al. 2012). As a rough speculation, frequent ketamine pulses might blur selective “plasticity windows” herein, thus opposing sought effects (e.g. ketamine`s antidepressant response) and promoting adverse effects (e.g. addiction, delusional thinking). Mrs. K. may be an example for (oppositional) tolerance (Fava & Offidani 2011) in antidepressant response, which could have developed after a critical amount of ketamine injections. To counteract, she further increased the dosage and frequency of ketamine injections, thereby perhaps promoting sensitization of chemical routes within the “addiction window”, which clinically may be expressed by the occurrence of craving for ketamine (Trujillo et al. 2011) being reliably reported to be the main feature of ketamine dependence and ketamine withdrawal syndrome (Jansen & Darracot-Cankovic 2001; Wollff & Winstock 2006; Kalsi et al. 2011; Morgan & Curran 2012; Bokor & Anderson 2014). The hypothesis of tolerance in antidepressant actions is generally a matter of debate and boosted by various clinical observations (Fava & Offidani 2011).

Another hypothesis is that Mrs. K`s escalating ketamine use placed on beyond the narrow antidepressant-dose response range observed in the preclinical ketamine literature. In rodent models of depression, ketamine's antidepressant-like behavioral and biochemical response is observed within a narrow range (1-~30 mg/kg intraperitoneal injection) - at higher, yet anaesthetic doses, ketamine's antidepressant

efficacy is lost resulting in an inverted U/parabolic dose-response curve (Li et al. 2010; Autry et al. 2011; Chowdhury et al. 2012). Similarly, as Mrs. K. escalated her dose to anaesthetic levels, ketamine's antidepressant efficacy might have been lost. However, there was no depression on the second admission of Mrs. K. being under the influence of clearly anaesthetic-like doses (up to 2g/day IM, c.f. K2 in Figure 1), what did not support this hypothesis in Mrs. K´s case.

Route of administration, dosage and adverse effects

Compared to 40 min lasting ketamine infusions, the IM route provides similar bioavailability (Table 1), a plasma peak within 5 minutes post injection and requires less monitoring (Irwin et al. 2013; Marland et al. 2013; Chilukuri et al. 2014). Glue et al. described an earlier occurring and greater plasma peak subsequent to ketamine 0.5 mg/kg IM than with 0.5 mg/kg IV (given as slow infusion over 40 min) in two women (Glue et al. 2011). A recent comparative study found that ketamine 0.25 mg/kg IM was just as effective and tolerable as ketamine 0.5 mg/kg IM or ketamine 0.5 mg/kg IV (the latter being administered over 40 min) in treatment resistant depressives; ketamine`s antidepressant response survived over 3 days and adverse reactions were rare, all mild and lasted less than an hour post injection (Chilukuri et al. 2014). One case report described a dose-dependency of the antidepressant response to ketamine IM-injections (0.5-1.0 mg/kg) (Glue et al. 2012). A female with bipolar depression responded to ketamine 50-70 mg IM administered over 4 months every fourth day (Cusin et al. 2012). Another female patient with bipolar depression developed a recurrence (Nierenberg & DeCecco 2001) at 6 months receiving ketamine 50 mg IM also every fourth day (Cusin et al. 2012). Ketamine 100 mg IM was not tolerated by the latter patient due to unpleasant dissociation (Cusin et al. 2012). Two other females with refractory depression, who initially did not respond to ketamine 0.5 mg/kg IM, improved with higher doses (0.7 and 1.0 mg/kg IM) for a few days, which were well tolerated (Glue et al. 2011). Another female with refractory depression received more than 40 slow ketamine infusions (0.5mg/kg) minimum twice a week and showed no cognitive abnormalities in MOCA or signs of dependence (Blier et al. 2012).

Mrs. K. wanted to stop her antidepressant dose of ketamine 200-400 mg (2.8-5.6 mg/kg) IM due to unpleasant dissociation, feeling of emptiness and cognitive impairment. 5 times higher daily doses divided into several sittings were reported on

recreational use of ketamine IM, both in lay persons (Pal et al. 2002) and professionals (Goyal et al. 2014) to counteract rapid tolerance in ketamine`s acute pleasant psychoactive effects (Wolff & Winstock 2006; Pal et al. 2002; Goyal et al. 2014). Those high daily ketamine doses were also achieved by Mrs. K. in her "exacerbated addiction modus" and were described to be associated with hazardous adverse effects (Jansen 2000; Pal et al. 2002; Wolff & Winstock 2006; Kalsi et al. 2011; Goyal et al. 2014). The preferred route of recreational use, however, is snorting ketamine as crystal powder, 100-400 mg per dose (Wolff & Winstock 2006).

Antidepressant alcohol after-effect?

Alcohol consumption is well recognized as having mood-enhancing properties (Cooper et al. 1992). Remarkably, Mrs. K. reported some longer lasting relief of her depression even after having used alcohol. At the beginning of her major depressive disorder alcohol seemed to be more effective than later on, pointing to the development of a tolerance in producing depression relief. Experiences like that are not unusual in the history of depressives and may facilitate a co-occurring or "secondary" alcohol addiction. In the light of the current ketamine research (Duman et al. 2012, Naughton et al. 2014) the question arises, whether alcohol ingestion can have also an antidepressant after-effect (Bonnet & Scherbaum 2015). This might be blurred by hangover and withdrawal symptoms, and might be less pronounced than ketamine`s antidepressant effect - possibly due to ethanol`s somewhat weaker antagonist action on glutamate NMDA-receptors and stronger agonistic effect on GABA-A-receptors than those of ketamine (Mion & Villevieille 2013; Tabakoff & Hoffman 2013). There are a couple of further striking pharmacological characteristics, which ketamine shares with ethanol and that are currently discussed to be involved in the mechanisms of ketamine`s antidepressant response (Duman et al. 2012, Naughton et al. 2014), such as

i) modulation of cortico-limbic dopamine (Lindefors et al. 1997; Moghaddam et al. 1997; Tabakoff & Hoffman 2013, Sleigh et al. 2014) and opioid pathways (Krystal et al. 2006; Mion & Villevieille 2013; Tabakoff & Hoffman 2013; Shenoda 2014, Sleigh et al. 2014);
ii) amplification of glutamate non-NMDA receptor signaling in cortico-limbic synapses (Krystal et al. 2006; Duman et al. 2012; Marty & Spigelman 2012);

iii) increased neurotrophin (BDNF, NGF) levels after acute administration (Logrip et al. 2009; Kavalali et al, 2012) and decreased neurotrophin levels during prolonged intake (Ke et al. 2014; Zhou et al. 2014);

iv) inhibition of synaptic long-term potentiation of hippocampal neurons which persisted after the drug`s washout (Zorumski et al. 2014; Izumi et al. 2014; Ribeiro et al. 2014);

v) activation of mammalian target of rapamycin function (mTOR)-signaling pathways (Duman et al. 2012; Sabino et al. 2013; Neasta et al. 2014);

vi) raising the number and size of dendritic spines in rodent hippocampal and prefrontal neurons (Carpenter-Hyland & Chandler 2007; Duman et al. 2012).

Intriguingly, chronic intermittent alcohol exposure to rats was associated with an increase in dendritic spine density in prefrontal pyramidal neurons that occurred precisely within one week after alcohol cessation (Kim et al. 2015; McGuier et al. 2015). That seems to be similar to alterations in spine morphology being found after a single, low dose of ketamine (Duman et al. 2012; Duman & Duman 2015). Spine synapses are considered to be the primary postsynaptic sites for dynamic morphological plasticity of excitatory glutamatergic neurotransmission (Duman & Duman 2015). It should be a further challenge to investigate whether low dosed single and repeated alcohol pulses could be followed by antidepressant responses in rodent models, such like ketamine (Duman et al. 2012; Duman & Duman 2015). Previous work demonstrated that low doses of ethanol were associated with antidepressant-like effects in Porsolt`s swim test on mice (Hilakivi et al. 1989).

Unquestionably, frequent at risk drinking of patients with depression is reliably associated with worse clinical and functional outcomes as well as with increasing health care utilization (Sullivan et al. 2005). This should also applied to ketamine when this drug`s therapeutic actions have been already overridden by its adverse effects as demonstrated in the case of Mrs. K.

Conclusion

The challenge remains to find the best way to a sustained antidepressant response to ketamine taking account of several pitfalls, among them the development of tolerance (even in ketamine`s antidepressant response) and dependence.

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