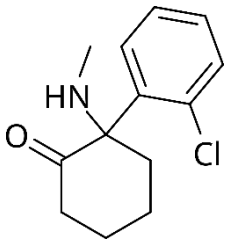
2-6-2021

The influence of ketamine on traffic safety

A review paper



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Abstract

Traffic accidents are a problem that almost every country in the world has to deal with. In The Netherlands alone 661 people have died and about 21,400 were severely injured as a result of these accidents in 2019. Psychoactive substances like ketamine are very likely to increase these risks of traffic accidents. About 0.6% of Dutch people in general in 2016 and 12.3% of Dutch people visiting bars in 2019 have used ketamine. Other countries like China (Hongkong), England and Wales also report people driving under the influence of ketamine which can result in traffic accidents. To study the influence of ketamine on driving multiple research questions have been formulated, namely:

- Is there a causal relationship between the amount of drug in blood/plasma of (recreationally used) ketamine in the driver and the ability to drive?
- Are there examples of legally bound limits for ketamine in plasma/blood in European countries and countries outside Europe regarding traffic safety? And on which research are these limits based?
- What maximum plasma/blood concentrations should be the legally bound limit for ketamine use by drivers?

To answer these research questions a literature review has been done. All relevant literature regarding ketamine is found via Pubmed and consists only of scholarly sources with the primary focus on recent sources which are less than 5 years old. Older sources have also been used because not all research has been reproduced or is only reviewed or cited in more recent literature. All literature cited about ketamine is from scholarly grade articles and are deemed reliable in nature. The focus of this literature review is on sources which have been cited often to give an overview on the ketamine research field. Research about the downstream neurological effects, isomeric effects and the effects of all the different metabolites formed of ketamine were found to be scarce.

Based on the information gathered in this literature review it has been confirmed that there is a causal relationship between the amount of drug in blood/plasma of (recreationally used) ketamine in the driver and the ability to drive. Non-fatal traffic accidents are reported with ketamine use and studies using mental tasks show significant reduction in functioning at concentration of >50 µg ketamine per liter plasma, but there is also some interpersonal difference with ketamine use.

Examples of European countries with legally bound limits for ketamine in plasma/blood regarding traffic safety are Norway, England and Wales. These ketamine limits are 55 µg/L in Norway and 20 µg/L in England and Wales. These limits are established from research reports which were conducted in these respective countries ranging from the lowest impairment limit of 44 µg/L ketamine to 200 µg/L limit per liter of whole blood. Countries which have a zero-tolerance policy for ketamine include Estonia, Poland, Slovenia, China (Hongkong), Australia, Canada and 21 States in the USA. Countries with graded sanctions for drug traces and driving under the influence of ketamine include Belgium, Germany, Latvia, Luxembourg and Finland. The Netherlands has a zero limit for using multiple drugs or a drug and alcohol while driving.

Based on the available literature, the maximum plasma/blood concentrations which should be the legally bound limit for ketamine use by drivers would be in the range of 44 µg/L to 200 µg/L ketamine in whole blood. With the lowest dose being 35 mg ketamine which can still cause a loss of driving ability, average physiological and pharmacokinetics parameters and a maximum time of 60 minutes of effect with intranasal ketamine use the best educated guess would be a maximum plasma/blood concentration of 36.5 µg/L which should be the legally bound limit for ketamine use by drivers.

Contents

1. Introduction

In The Netherlands 661 people have died and about 21.400 were severely wounded as a result of traffic accidents in 2019 alone. The largest groups of traffic participants that were affected are car drivers and cyclists which both amount to about a third of the cases (CBS, 2020). Research among car drivers in The Netherlands has shown a detected substance prevalence of 2.2% for alcohol, 2.2% for drugs of abuse, 0.6% for prescription drugs and 0.6% for a combination of all substances (Mütze, 2017). Furthermore, the relation between alcohol consumption and psychoactive substance use resulting in an increased risk of a traffic accident is widely studied and acknowledged (Smink et al., 2005). One of these psychoactive substances that has become popular in The Netherlands is ketamine, a compound that is known for its anesthetic and hallucinogenic properties. A survey from the Leefstijlmonitor found that 1.2% of Dutch adults had used ketamine in their lifetime and 0.6% in 2019. Among young adults and people going to bars ketamine use is much higher, 17.3% has used ketamine in their lifetime and 12.3% in 2016 (Trimbos instituut, 2019).

Several studies outside The Netherlands involving driving and ketamine use have become available in the past decade. A study from Hongkong, a city with a high prevalence of ketamine users, showed a 45% ketamine prevalence among intoxicated drivers involved in non-fatal traffic accidents in 2007 (n=38) (Wong et al., 2010). A study from Australia tested driver performance in a driving simulation after receiving a 0.3 mg/kg intravenous bolus dose of ketamine followed by a 0.15 mg/kg/h continuous infusion of ketamine for 1.5 hours. The visual analog scale for alertness, being clear headed, coordination, mental ability and attention all showed a significant decrease in functioning compared to baseline driving abilities (Hayley et al., 2019). A study involving suspected drugged drivers (by committing one or more traffic offences) in England and Wales found 14 cases out of 376 to be drivers under the influence of ketamine and norketamine with mean concentrations of 421 ng/mL and 605 ng/mL, respectively (n=295) (Burch et al., 2013). However, determining the prevalence of ketamine as a drug of abuse among car drivers in severe accidents is difficult if the possibility exist that crash victims receive emergency life-saving treatment by this anesthetic, as is the case in Sweden (Jones et al., 2009).

To study the influence of ketamine on driving multiple research questions have been formulated, namely:

- Is there a causal relationship between the amount of drug in blood/plasma of (recreationally used) ketamine in the driver and the ability to drive?
- Are there examples of legally bound limits for ketamine in plasma/blood in European countries and countries outside Europe regarding traffic safety? And on which research are these limits based?
- What maximum plasma/blood concentrations should be the legally bound limit for ketamine use by drivers?

2. Literature review method

All relevant literature regarding ketamine is found via Pubmed and consists only of scholarly sources with the primary focus on recent sources which are less than 5 years old. Literature older than 5 years is also used, because a lot of research regarding ketamine has been done in the 80's, 90's and early 2000 and has not been reproduced or is only reviewed or cited in more recent literature. The search engine of Pubmed functions by putting more relevant and more often cited sources at the top after searching for specific keywords. These more popular and cited sources were preferred and were regarded as more reliable to give an overview on the ketamine research field. Keywords used include "driving", "neurology", "pharmacokinetic", "pharmacodynamic", "limit", "NMDA receptor" and "cognitive impairment" combined with the word ketamine. Sources used for finding laws about ketamine worldwide were found using the google search engine. These sources about ketamine legislation need to be from scholar origin, from official state or country government websites or up-to-date law firm websites which are practicing law in that state or country. The sources used for this literature review are also selected to best answer the formulated research questions.

With the used method for searching literature the most important literature about ketamine is used instead of all literature available (which would be about 21,000 papers more or less). It has to be noted that a lot of the available literature is not appropriate since ketamine is most commonly used as an anesthetic for animals. Although this information is interesting the (less prevalent) sources including people cover the physiological topics of ketamine more than enough. Another aspect is the amount of research that has been done with ketamine in humans. On one hand there is plenty of research done about for example the anesthetic properties, but much less is known about the downstream neurological effects, isomeric effects and the effects of all the different metabolites formed. Sources were selected based on the mentioning of human data and were excluded when mentioning anesthesia (except for 1 source, mentioning subanesthetic is allowed), since anesthetic ketamine concentrations are not in the range of recreational ketamine use. From this pool of 6,000 papers the most relevant and useful were used for this report.

3. The neurology of driving and ketamine

Driving involves multiple neurologic systems that need to function adequately and include higher cognitive functioning, vision, motor control, intact coordination, and an ability to maintain attention. Higher cognitive functions needed for driving are interpretation of situations, recalling previous experiences, formulation of a plan and monitoring the outcome of the behavior (Drazkowski & Sirven, 2011). Brain regions involved in driving include somatosensory cortex (Brodmann area's 1, 2 and 5), motor and premotor cortex (Brodmann area's 4 and 6), parietal cortex (Brodmann area's 5 and 7), visual cortex (Brodmann area's 18 and 19) and the cerebellum (V.D. Calhoun & Pearlson, 2012; Vince D. Calhoun et al., 2002; Graydon et al., 2004; Spiers & Maguire, 2007; Uchiyama et al., 2003; Walter et al., 2001). When distracted while driving or when speeding the frontal polar region (Brodmann area 10), ventrolateral and dorsolateral prefrontal cortex (Brodmann area's 9, 46 and 47) may play an active role. (Jäncke et al., 2008; Schweizer et al., 2013).

Ketamine is found to disrupt a lot of these neurological systems like sustained and divided attention, motor and executive functions, eye movements and visual search, working memory, perceptions, perception of time and information processing at concentrations >50 µg ketamine per liter plasma (Giorgetti et al., 2015). One study exposed healthy volunteers to plasma concentrations of 0, 50, 100, 150, and 200 µg/L ketamine which were for 30 min maintained. After 20 minutes these volunteers performed a 13-step test including questions about their vision, the passing of time and drowsiness. They found that the relation between steady-state plasma ketamine concentrations and effects was highly linear between 50 and 200 µg/L (Bowdle et al., 1998). It should however be noted that the high linearity of at least the "high" scale is based on averaged data points, see figure 1. The individual data points would only indicate a somewhat linear relationship with R>0.50. Furthermore, the interpersonal differences seem to increase in the higher dosing range (<50 ng/mL ketamine plasma concentration).

A more recent study measured the dissociative symptom levels in healthy subjects (N=99) receiving a single IV dose of 0.1 mg/kg ketamine, 0.2 mg/kg, 0.5 mg/kg, 1.0 mg/kg or 0.045 mg/kg midazolam (active placebo). Measurement points were at 5, 40, 80 and 120 minutes after infusion. The average Clinician-Administered Dissociative States Scale (CADSS) score of the 0.5 mg/kg (14 score) and 1.0 mg/kg (24.5 score) ketamine doses were significantly higher than the active placebo (2.5 score) after 40 minutes. The lowest significant dose of 0.5 mg/kg would translate to 44 µg/L ketamine with average physiological parameters. Lower ketamine doses were not significantly different. After 80 minutes the high dose ketamine scores were also no longer significant different, which indicates a clear dose-response curve (Fava et al., 2020).

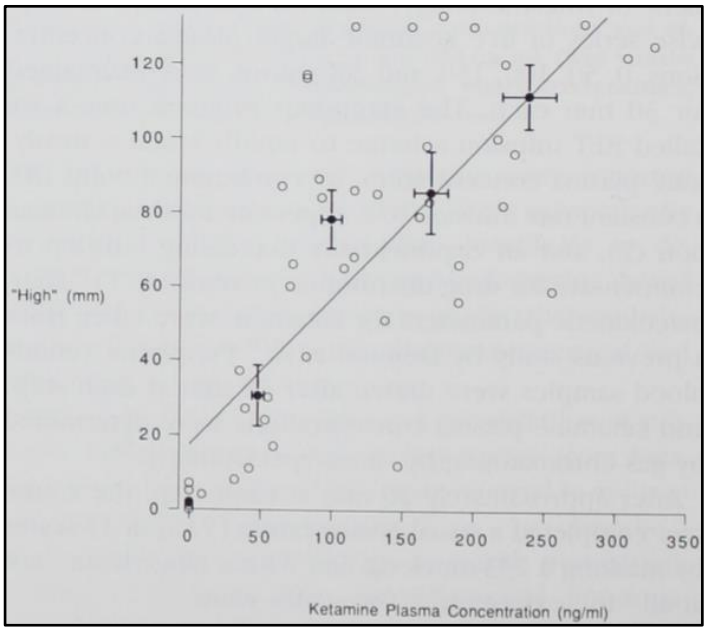

Figure 1: The visual analog score for scale item HIGH ("I felt high") (from values 0 to 133 meaning not at all to extremely) are plotted versus ketamine plasma concentrations. Open circles represent one pair of data points, closed circles are the mean values for each target concentration of 0, 50, 150 and 200 ng/mL. R was found to be 0.96 with a P value of 0.01, most likely based on the mean data points of 50, 150 and 200 ng/mL (Bowdle et al., 1998).

4. Pharmacokinetics of ketamine

Ketamine is a fast-acting anesthetic used in humans and animals. It consists of a racemic mixture of both arketamine and esketamine. Of all the routes ketamine can be administered, it is usually delivered via injection at anesthetic doses and insufflated and orally taken when used recreational (Félix et al., 2016). Recently, a nasal spray containing only esketamine was approved by the food and drug administration (FDA) and European Commission (EC) for treatment-resistant depression (FDA, 2019b). A typical ketamine dose is 1-2 mg/kg intravenous (IV) and 2-4 mg/kg intramuscular (IM) for an anesthetic effect and 60-250 mg nasal and 200-300 mg oral for recreational use. The bioavailability of ketamine is intramuscular (IM) 93% (Clements et al., 1982), intranasal 45% to 50% (Malinovsky et al., 1996; Yoshitsugu Yanagihara et al., 2003) and orally 17-25% (Kalsi et al., 2011; Pai & Heining, 2007). Oral bioavailability is reduced compared to other delivery routes due to extensive first pass metabolism in the liver.

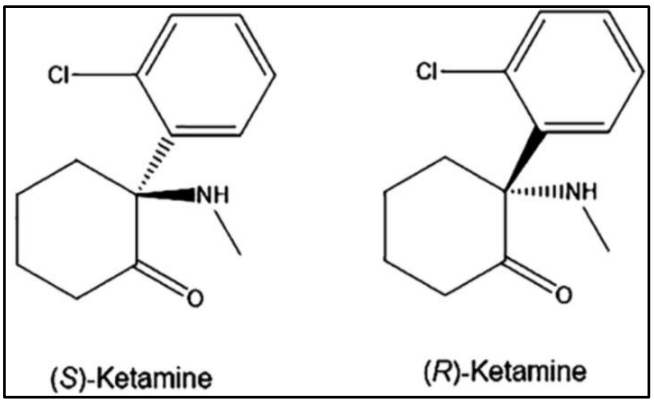

Figure 2: ketamine is most commonly used as a racemic mixture of (S)-ketamine and (R)-ketamine (Hashimoto, 2019)

The volume of distribution of ketamine is 3 to 5 L/kg after IV with a plasma protein binding between 10% and 50% (Dayton et al., 1983; Karch & Drummer, 2015; Peltoniemi et al., 2016). The distribution half-life is thought to be about 11 minutes after intravenous administration, but times as low as under 5 minutes have also been documented (Edward F Domino et al., 1984; Wieber et al., 1975). Maximum plasma concentrations are 1-5 minute after IV and IM administration, 20 minutes intranasal and 30 minutes oral. The onset of action of ketamine is 5 to 10 minutes after internasal administration and may last for 45 to 60 minutes, if taken orally however the onset is after 15 to 20 minutes and may last for as long as 4 to 6 hours (Félix et al., 2016). The blood plasma partitioning ranges from 0.97 – 1.07 in humans for ketamine (Tran et al., 2018).

Metabolism of ketamine occurs mainly in the liver and is stereoselective (Chang & Glazko, 1974). The major metabolic pathway is N-demethylation to the less active metabolite norketamine by CYP3A4 (White et al., 1982). The second step of the major metabolic pathway is hydroxylation of norketamine by CYP2B6 and CYP3A6. A minor pathway of non-enzymatic dehydroxylation of hydroxy-norketamine results in dehydro-norketamine which still shows a bit activity (Paul et al., 2014). Both ketamine and norketamine can be hydroxylated and glucuronidated to inactive forms which also facilitates urinary excretion (Dinis-Oliveira, 2017; Schmitz et al., 2009; Y Yanagihara et al., 2001).

The elimination half-life of ketamine is about 2 to 4 hours by intravenous route (E F Domino et al., 1982). Ketamine and metabolites are renally cleared of which 2% is ketamine, 2% norketamine, 16% dehydronorketamine and 80% hydroxylated ketamine conjugated with glucuronic acid (Adamowicz & Kala, 2005; Karch & Drummer, 2015).

Pharmacokinetic interactions with ketamine are possible since ketamine is metabolized by CYP enzymes, but ketamine can also have an effect on other CYP enzymes. Diazepam for example is a substrate for CYP3A4, the enzyme needed for the first step in the major metabolic pathway from ketamine to norketamine. One study has shown that 10 minutes before ketamine dosing taking 0,3 mg/kg diazepam results in about a 1 minute and 40 seconds increase in distribution half-life and a 15 minutes increase in elimination half-life (Edward F Domino et al., 1984). In another study subjects received the CYP inducer rifampicin (CYP3A4 and CYP2B6 among others), 600 mg daily, and oral

esketamine (0,29 mg/kg/h or 0,57 mg/ kg/h) which resulted in a 10% and 50% reduction in the area-under-the-curve of the plasma concentrations compared to the placebo group, respectively (Noppers et al., 2011). An in vivo study in rats has shown that ketamine (80 mg/kg) induces multiple forms of CYP enzymes including CYP1A, CYP2B, CYP2E1 and CYP3A by a 2, 13, 2 and 2 fold, respectively (Chan et al., 2007).

Besides the emergence of ketamine as designer drugs, there are also new forms of ketamine being designed that are not yet outlawed and have potentially stronger physical effects. These compounds include Deschloro-N-ethyl-ketamine (2-oxo-PCE), Deschloroketamine (DCK), 2-Fluorodeschloroketamine (2FDCK) and Methoxetamine (MXE), most of which are already found in Hongkong (Botanas et al., 2019; Li et al., 2019). These compounds consist of a combination of removing or substituting the chloride group with fluoride or a methoxy group and substituting the N-methylamino group with a N-ethylamino group. The drug 2-oxo-PCE is found to cause a similar effect to ketamine, but is more potent. This ketamine derivate has been recently reported in Germany (Chong et al., 2017). Not long ago there was a fatal case involving a 52-year-old man who was found dead in the bedroom and had abused 2-oxo-PCE and the antidepressant venlafaxine prior to his death. The highest concentration drug was observed in the liver (6.137 ng/g) (Theofel et al., 2019). The ketamine derivatives DCK and 2FDCK consist of a ketamine molecule with a removed chloride group and an added fluoride group which substitutes the chloride group, respectively. This difference in halogen is found to have an influence on the binding properties to CYP2B6. Theoretical modelling indicates that the removal of the chloride group prevents DCK (K_m 184 ± 18) from binding with CYP2B6. The substitution of chloride by the fluoride group only lowers the binding potential of 2FDCK ((K_m 40 ± 3) to CYP2B6, but does not prevent it (Wang et al., 2019). A reduction in clearance of ketamine derivatives could result in a longer lasting effect. The MXE molecule is constructed similar as the 2-oxo-PCE molecule which both have a substitution of the N-methylamino group with an N-ethylamino group. This chemically alteration is thought to increase potency and duration of action. The chloride group substituted by a methoxy group is thought to reduce analgesic and anesthetic properties of MXE which could increase the abuse potential of this drug compared to ketamine (Zanda et al., 2016).

5. Pharmacodynamics of ketamine

When racemic ketamine arrives at the N-methyl-D-aspartate (NMDA) receptor the different isomeric properties become important. Ketamine is an uncompetitive antagonist for the NMDA receptor to which it binds allosteric. Arketamine has an inhibition constant (K_i) value of 1.40 µM for this receptor, whereas esketamine has a lower K_i value of 0.30 µM. The racemic combination of the two stereoisomers is found to have a K_i value of 0.53 µM for the NMDA receptor (Hashimoto, 2020). The resulting effect of ketamine blocking NMDA receptors is complex because of the wide spread of NMDA receptors in the central nervous system. NMDA receptors are thought to be present on GABAergic inhibitory interneurons (disinhibiting effect), extra-synaptic on postsynaptic neurons (inhibiting effect), synaptic on postsynaptic neurons (inhibiting effect) and on presynaptic glutamatergic neurons in the lateral habenula (inhibiting effect) (Zanos & Gould, 2018).

Structurally, NMDA receptors (NMDARs) are heterotetramers which consist of 2 subunits GluN1 and either 2 subunits of GluN2(A-D) and/or GluN3(A and B) (see figure 3). The binding position of both ketamine and MK-801 (also known as dizocilpine) are thought to be on the ubiquitous GluN1 subunit in the transmembrane domain (TMD) very near to the center of the ion channel (Karakas et al., 2015; Lee et al., 2014). MK-801 is a NMDA receptor antagonist like ketamine, but is not widely used due to possible neurotoxicity. The neurotoxicity of this compound is most likely caused by blocking NMDA receptors for to long. Neurotoxicity caused by ketamine is also thought to be possible with prolonged exposure of a high dose in infants, however ketamine is also known to have neuroprotective effects (Yan & Jiang, 2014). For ion channels of NMDARs to open both glutamate needs to be bound to the receptor and magnesium ions (Mg^{2+}) on the receptor need to be unbound due to cell depolarization. This causes the free flow of calcium (Ca^{2+}) and sodium (Na^{+}) ions into the cell and potassium (K^{+}) ions out of the cell (Purves et al., 2007).

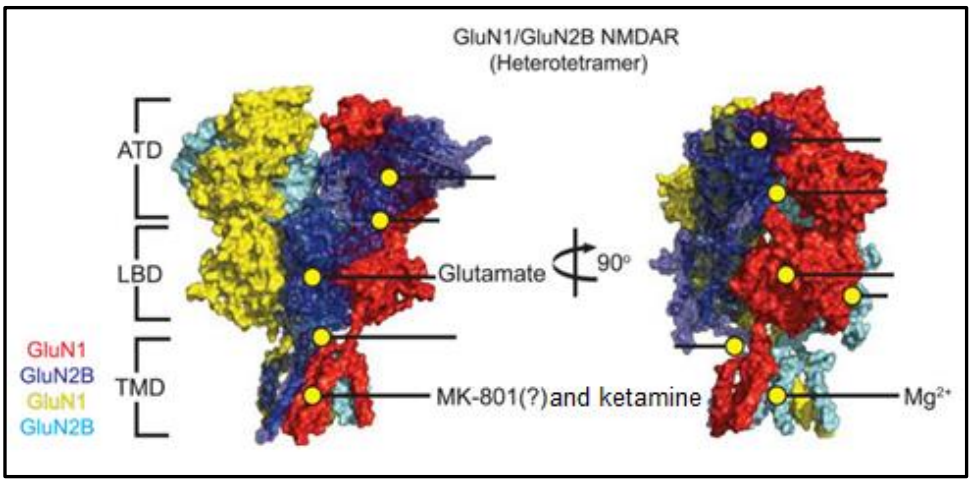

Figure 3: A three-dimensional image of a N-methyl-D-aspartate receptor (NMDAR) consisting of 2 subunits GluN1 and 2 subunits GluN2B as a heterotetramer. The receptor is viewed sideways from two different positions, rotated 90 degrees clockwise. The upper region of the receptor is called the amino terminal domain (ATD), the middle part consists of the ligand-binding domain (LBD), the lower part, which is inside the cell membrane, is the transmembrane domain (TMD). On the inside of the cell there is also the carboxyl terminal domain attached to the receptor (TMD), but this is not shown. Yellow dots represent ligand binding sites of which the most relevant are shown: glutamate needed for activation of the receptor, Mg^{2+} which is blocking the ion channel during resting membrane potential and MK-801 also known as dizocilpine that shares the binding location on the receptor with ketamine (Karakas et al., 2015; Lee et al., 2014) .

It is suggested that ketamine may have dopaminergic effects, because its use as a drug of abuse. A meta-analysis of acute effects of sub-anesthetic ketamine dosing in rodents showed significant increases in dopamine levels in the cortex, striatum and nucleus accumbens compared to control conditions (Kokkinou et al., 2018). Furthermore a 62-180% increase in dopamine neuron population activity, like in the frontal cortex and the ventral tegmental area, was also found (Belujon & Grace, 2014; El Iskandrani et al., 2015; Witkin et al., 2016). Chronic sub-anesthetic ketamine dosing in rodents was associated with consistent dopamine level elevation (88-180%) in the frontal cortex (Chatterjee et al., 2012; Lindefors et al., 1997; Tan et al., 2012).

One study showed that administering ketamine intraperitoneal in mice (10 mg/kg) induced extracellular serotonin levels in the prefrontal cortex and dorsal raphe nucleus. (Pham et al., 2017). This could possibly be attributed to ketamine inducing the inhibition of serotonin reuptake, as is shown in another in vivo study with 80 mg/kg ketamine in rodents (Martin et al., 1982). This interaction of ketamine with the serotonergic system however is thought to be indirect since ketamine does not have an agonist or antagonist effect on serotonin transporters (SERTs) (Zanos & Gould, 2018).

Based on the pharmacodynamics of ketamine it is very likely that the antagonistic effects of ketamine on NMDA receptors is responsible for the loss of driving ability. Since the binding of racemic ketamine is about 40% higher to this receptor compared to esketamine, a higher dose of esketamine would be needed for the same loss of driving ability as when ketamine is used.

6. Ketamine limits for driving abroad

One of the few countries in Europe with a limit for ketamine in blood while driving is Norway. The legally allowed limit is set on 55 µg ketamine per liter of whole blood. This is in part based on The Norwegian Academic Advisory Group (2010) which suggested a prohibition limit in blood of 48 µg/L for ketamine (European Commission, 2016; WOLFF et al., 2013). Another study on which the Norwegian ketamine limit is based worked with the following parameters. When ketamine is intravenously administered the impairing drug dose is 35 mg. This dose would translate to an impairing drug dose of about 70 mg ketamine intranasal. The impairment limit in whole blood was found to be 55 µg/L, which is comparable to 0.02% BAC (blood alcohol concentration). For graded sanctions comparable to 0.05% BAC and 0.12% BAC in whole blood, 137 µg/L and 329 µg/L ketamine were advised, respectively (Schmid et al., 1999; Vindenes et al., 2012).

The countries England and Wales within the United Kingdom (UK) also have regulation regarding ketamine limits while driving. They assume that exposure to illegal drugs can occur accidental and combine that with a zero-tolerance approach. Because of this reasoning the ketamine limit is set a bit lower, on 20 µg per liter of blood (Department for Transport, 2017). A report from the expert panel on drug driving commissioned by the Department for Transport advised the UK about the ketamine limit at the time. These experts recommended a threshold limit in whole blood for ketamine of 200 µg/L and a threshold limit in whole blood for ketamine when detected in combination with alcohol of 100 µg/L. The legal ketamine limit is therefore 10 times lower than was advised (WOLFF et al., 2013). A research paper cited in the report from the expert panel on drug driving found a lowest impairing concentration of ketamine of 113 µg per liter of plasma (Morland & Strand, 2010).

European countries which have a zero-tolerance policy for driving with any trace of psychoactive compounds include Estonia, Poland and Slovenia. Other European countries like Belgium, Germany, Latvia, Luxembourg and Finland distinguish the presence of drug traces in drivers and driving under the influence. The former is punishable by a small fee while for the latter more severe sanctions are given (Europees Waarnemingscentrum voor drugs en drugsverslaving, 2009). The Netherlands has a zero limit for using multiple drugs or a drug and alcohol while driving (Rijksoverheid, 2017). This limit is based on the lowest reliable measurable amount of component which is not endogenous.

Non-European countries which have a zero-tolerance policy regarding ketamine are China (Hongkong), Australia and Canada. Both China (Hongkong) and Australia do not allow any concentration of ketamine to be present in blood while driving (Alcohol and Drug Foundation, 2020; The government of Hongkong, 2020). In Canada it is prohibited to have any detectable amount of ketamine present in blood within two hours of driving (Department of Justice, 2019). Although drug driving laws can differ between States the Food Drug Administration (FDA) in the United States recommend not to drive on the day of ketamine use and advises to drive the following day after a restful sleep (FDA, 2019a).

The following 29 States do not have zero-tolerance laws for drugs: Alabama, Alaska, Arkansas, California, Connecticut, District of Columbia, Florida, Hawaii, Idaho, Kansas, Louisiana, Maine, Maryland, Massachusetts, Mississippi, Missouri, Nebraska, New Hampshire, New Jersey, New Mexico, New York, North Dakota, Oregon, South Carolina, Tennessee, Texas, Vermont, West Virginia and Wyoming. The following 21 States do have a form of zero-tolerance laws for drugs: Arizona, Colorado, Delaware, Georgia, Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota, Montana, Nevada, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Dakota, Utah, Virginia and Wisconsin (GHSA, 2021). The state laws of Georgia and Minnesota specify that the zero-tolerance policy has to be combined with unsafe driving for it to be penalized (Kans Law Firm, 2021;

Lawson, 2016). In states of Colorado, Illinois, North Carolina, Oklahoma the zero-tolerance policy is for people under the legal drinking age of 21 years (Green, 2021; Ktenas law, 2021; OHSO, 2021; Schwaner, 2021).

7. Discussion and Conclusion

All literature cited about ketamine is from scholarly grade articles and are deemed reliable in nature. There are however still a lot of unknowns with ketamine use for which more research needs to be conducted and published, especially about downstream neurological effects, isomeric effects and the effects of all different metabolites formed. It should be noted that the usable pool of literature to answer the research questions is much smaller than all ketamine literature available because a lot of the research is focused on the anesthetic effects of ketamine on different animal species.

The research questions formulated to study the influence of ketamine on driving are:

- Is there a causal relationship between the amount of drug in blood/plasma of (recreationally used) ketamine in the driver and the ability to drive?
- Are there examples of legally bound limits for ketamine in plasma/blood in European countries and countries outside Europe regarding traffic safety? And on which research are these limits based?
- What maximum plasma/blood concentrations should be the legally bound limit for ketamine use by drivers?

To answer the first research question, there is without a doubt a causal relationship between the amount of drug in blood/plasma of ketamine in the driver and their ability to drive. Ketamine users are over-represented in traffic accidents in for example Hong Kong. Studies using visual analog scales show a decrease in driving ability functioning and an increase in feelings of anxiousness, drowsiness, highness and changes in colors, sound, surroundings and time perception. Moreover, other studies mention problems with sustained and divided attention, motor and executive functions, eye movements and visual search, working memory, perceptions, perception of time and information processing at concentration of >50 µg ketamine per liter plasma, which is in the range of what recreational ketamine users would take. The linearity of these effects caused by ketamine use however is not entirely certain. Literature mentioning linear ketamine use is sparse and upon closer inspection still shows a lot of interpersonal differences of ketamine induced symptoms.

Worldwide only two ketamine limits can be found, the 55 µg/L ketamine limit in Norway and the 20 µg/L limit in England and Wales. These limits are established from research reports which were conducted in these respective countries. Research from Norway has found both a lowest impairment limit of 48 µg/L and 55 µg/L ketamine per liter of whole blood. The differences in ketamine concentrations in plasma and blood are deemed not significant, since the blood plasma partitioning of ketamine is found to range from 0.97 – 1.07 in humans. Experts from the UK advised a 200 µg/L limit for only ketamine in whole blood and a 100 µg/L limit for ketamine in the presence of alcohol in their report. A lowest impairing concentration of ketamine of 113 µg/L in plasma was also mentioned in one of the sources cited of these experts. The legal point of view of England and Wales was that exposure to illegal drugs can occur accidental and combine that with a zero-tolerance approach, which results in the lowest analytical reliable limit of 20 µg/L ketamine. Countries which have a zero-tolerance policy for ketamine include Estonia, Poland, Slovenia, China (Hongkong), Australia, Canada and 21 States in the USA. Countries with graded sanctions for drug traces and driving under the influence of ketamine include Belgium, Germany, Latvia, Luxembourg and Finland. The Netherlands has a zero limit for using multiple drugs or a drug and alcohol while driving.

The maximum plasma/blood concentrations which should be the legally bound limit for ketamine use by drivers is a difficult question to answer. Based on the available literature the impairment limit would be in the range of 44 µg/L to 200 µg/L ketamine in whole blood. With an average dose of 155

mg internasal, 50% bioavailability, 30% protein binding, an average volume of distribution of 4 L/kg and the average weight of 70 kg the peak ketamine concentration in whole blood would be about 195 µg/L. In this same scenario the lowest common reported dose of 60 mg ketamine intranasal would result in a maximum ketamine concentration in whole blood of 75 µg/L. One could argue that the lowest dose recreationally used would have some effect which is perceived beneficial for the user and hence makes the user less suitable for driving. This would further narrow the possible limit for maximum plasma/blood concentrations of ketamine to 44 µg/L to 75 µg/L ketamine in whole blood. It is reported that intranasal use of ketamine may last for a maximum of 60 minutes. With an elimination half-life of about 3 hours for ketamine by intravenous route this would translate to a 16,7% reduction in ketamine concentration in whole blood/plasma resulting in a concentration of 36,5 µg/L when the lowest concentration is used. Based on the available literature the best educational guess would be a maximum of 36.5 µg/L ketamine in whole blood/plasma which should be the legally bound limit for ketamine use by drivers. Additionally, the interpersonal variation at this ketamine limit is low. With this ketamine limit recreational ketamine users who have taken a low dose (60mg), average dose (155 mg) or high dose (250 mg) would have to wait about 3 hours, 7.25 hours or 9.5 hours respectively before driving.

8. References

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