Ketamine pharmacometrics

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General introduction

The phenylcyclohexylamine derivative ketamine was originally developed in the 1960s as a dissociative intravenous anesthetic agent, to replace phenylcyclohexylamine due to its severe side effects.[1] Because of the specific beneficial characteristics, such as the potent analgesic effects, the protection of the upper airway reflex and absence of clinically relevant respiratory depression, ketamine rapidly gained popularity. Interestingly, a renewed interest in ketamine has emerged in the recent years, because of new possible indications such as the treatment of treatment-resistant depression,[2] the management of different types of neuropathic pain, including chronic regional pain syndrome,[3,4] and the reversal of opioid-induced respiratory depression.[5]

However, despite the improvements in the side effect profile compared with its predecessor phenylcyclohexylamine, the wide application of ketamine is limited by serious side effects, including psychotomimetic and schizotypal effects.[1] In order to fully exploit the potential benefits of ketamine for new indications, a more thorough understanding is warranted concerning the relation between the pharmacokinetics and pharmacokinetics. However, due to the complex metabolism and the different ketamine forms currently available, the analysis of the relationship between ketamine pharmacokinetics and effects is a challenging journey.

MECHANISM OF ACTION

Historically, the N-Methyl-D-Aspartate receptor (NMDAR) was thought to be the primary receptor targeted by ketamine. Binding of ketamine to the NMDAR has been associated with its analgesic effects, but also with its dissociative anesthetic, amnesic and psychotomimetic effects.[1,6] However, more recent studies indicated that ketamine exerts its effects by binding, in addition to the NMDAR, to a wide range of receptor types including opioid receptors, sigma receptors, dopamine D_2receptors, muscarinic acetylcholine receptors, innate repair receptors and HCN1 cation channels, further adding to the complexity of ketamine pharmacodynamics.[1]

METABOLISM

Ketamine is mainly metabolized via cytochrome P450 (CYP) enzymes, of which CYP2B6 and CYP3A4 are the most important subtypes.[7,8] Although several metabolic pathways are described, the demethylation of ketamine to norketamine, with a subsequent conversion to either dehydronorketamine or hydroxynorketamine is considered to be the main metabolic pathway (Fig. 1).[9] Other, minor metabolic pathways include the hydroxylation of ketamine to hydroxyketamine and the conversion of ketamine to

hydroxyphenylketamine by CYP2C9 and flavin-containing mono-oxygenase enzymes. Furthermore, hydroxyketamine can be further converted to hydroxynorketamine.[1] Approximately 80% of the ketamine is converted to norketamine, 5% to hydroxyketamine and 15% to hydroxynorketamine.[6]

As shown in Fig 1, the cyclohexanone group of ketamine has an asymmetrical carbon, which implies that there are two types of ketamine: an *R*-enantiomer and an *S*-enantiomer. Originally, only the racemic mixture of *RS*-ketamine was marketed (Ketalar®). However, in 1997, the pure *S*-ketamine enantiomer was brought on the market as Ketanest®. Studies showed significant differences in pharmacokinetics and pharmacodynamics between those two ketamine enantiomers.[6,10-13] For example, *R*-ketamine elimination clearance has shown to be up to almost 50% lower than that of *S*-ketamine,[11-13] which might be explained by the lower affinity of CYP3A4 for *R*-ketamine compared to *S*-ketamine. Interestingly, CYP2B6 metabolizes both enantiomers with a nearly equal efficacy.[14] In addition to ketamine, stereo-selective metabolism is also likely to play a role in the formation and conversion of the metabolites.[15]

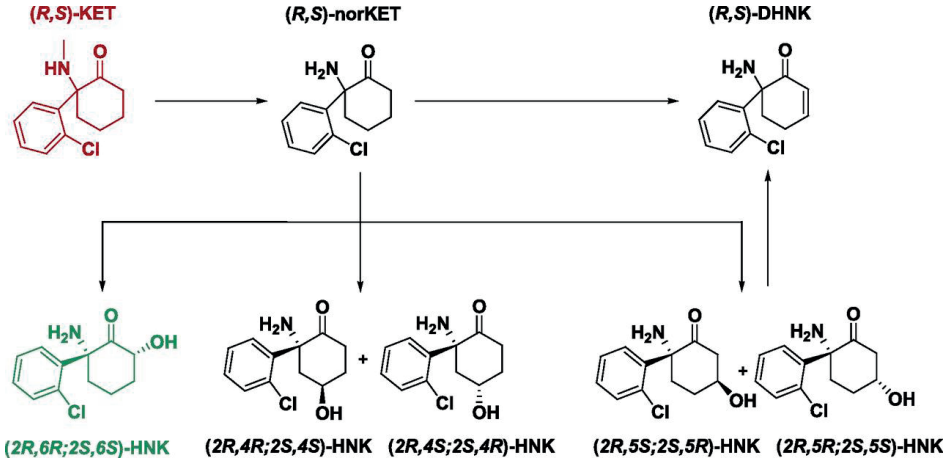

Figure 1. Main metabolic pathway of ketamine and metabolites. Ketamine (KET) is converted via CYP2B6 and CYP3A4 to norketamine. Norketamine is subsequently converted to either hydroxynorketamine (HNK) by hydroxylation or to dehydronorketamine (DHNK) by dehydrogenation. Note that norketamine can be hydroxylated at the four or the five position, resulting in different forms of hydroxynorketamine. Figure adopted from Zanos et al.[1]

THESIS OUTLINE

Although ketamine can be considered to be an "old" drug, a definitive model explaining ketamine pharmacokinetics for a wide range of patient populations, dosing regimens and ketamine administrations forms is lacking.[16] Currently, a large number of ketamine

population pharmacokinetic models is published.[17] However, the large number of ketamine pharmacokinetic models based on data from all types of study populations, ketamine dosing regimens and administration forms, can prove to become a serious challenge for clinical decision makers, since it may not always be easy to pick the model that best suits their patient population.

In this thesis, we focus on unraveling the complex pharmacokinetics and pharmacodynamics that characterize ketamine, in order to get a step closer to a final "all encompassing" pharmacokinetic-pharmacodynamic model. For the pharmacodynamic outcomes, we especially focus on the effects of ketamine on neuropathic pain, nociceptive pain (pressure pain) and psychedelic outcomes.

First, in **Chapter 2**, the role of ketamine for the treatment of neuropathic pain is studied. This chapter is an update of a previously published expert opinion, published in 2012.[18] In addition, the reader will be given some understanding of ketamine's complex metabolism.

Chapter 3 concerns a combined systematic review, meta-analysis and population pharmacokinetic modeling study that aimed to develop an overall population pharmacokinetic model for ketamine. Since a plethora of factors can influence pharmacokinetics, the effects of several important subject characteristics (weight, sex and adult *versus* pediatric, healthy *versus* patient populations) and different ketamine administration forms (*S*-ketamine, *R*-ketamine or *RS*-ketamine) are evaluated.

In **Chapter 4** the focus will remain on ketamine pharmacokinetics. However, in this chapter, stereoselective pharmacokinetic data on ketamine, norketamine, dehydronorketamine and total hydroxynorketamine obtained from randomized placebo-controlled double blind clinical study are analyzed using a nonlinear mixed effects modelling approach.

In **Chapter 5**, the cardiac output data obtained from the same study as described in Chapter 4 were analyzed by using a population pharmacodynamic modeling approach. The previously developed population pharmacokinetic model for ketamine, norketamine, dehydronorketamine and hydroxynorketamine was therefore expanded with a pharmacodynamic model to test the potential effects of each compound on cardiac output. Since potential differences in potency exist between *S*- and *R*- enantiomers for multiple pharmacodynamic outcomes,[19-22] we included an evaluation of the separate effects of *S*- and *R*-enantiomers on the cardiac output.

Finally, in **Chapter 6**, we aimed to develop a population pharmacodynamic model to describe the effects of *RS*-ketamine and *RS*-norketamine on the pressure pain threshold and psychedelic symptoms, defined as external perception.

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