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EDITORIAL

Ketamine for the treatment of (super) refractory status epilepticus? Not quite yet

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Status epilepticus (SE) is the most severe form of epileptic disorder. The International League Against Epilepsy (ILAE) considers that, depending on the type of SE, the duration of seizures used to define SE is different. For generalized convulsive SE, the most common and severe form, SE is considered after only 5 min of seizures and 30 min is considered to be the time after which the ongoing seizures have long-term consequences [1]. SE is thus a neurological emergency both in adults and in children as it could lead to seizure-related brain damage, to a wide array of pathological effects, and even to death if untreated. Although some data challenge the true association between SE duration and brain injury [2], adverse effects of seizures on cardiovascular and respiratory functions require quick action and initiation of pharmacological treatment. SE is reported to occur annually in ca. 10–40 per 100,000 people. The overall mortality rate in SE has been estimated to be around 20% (adults and children) from two US studies in Rochester and Richmond [3]. Causes for SE are numerous and could be the consequence of a preexistent epilepsy. Indeed, it is estimated that 5% of adults and 10–25% of children suffering from this disease will have at least one SE [4]. As a consequence of the short duration of seizures necessary before becoming SE, there is a race against time to diagnose the seizures and to treat them effectively before they become refractory to treatment. The ILAE also defines an established SE when it persists after use of a first-line agent (usually a benzodiazepine) and a refractory status epilepticus (RSE) as an SE that persists after first- and second-line agents (additional agent such as hydantoins, valproic acid, levetiracetam, and barbiturates) have failed [4]. First- and second-line pharmacotherapies are relatively consensual although the treatment algorithms could change depending on countries and medical facilities [5]. Numerous reviews are published every year but without really bringing clarity. If seizures are still not controlled, there is currently even less definitive data to guide the optimal choice of therapy. Treatment is usually based on a combination of several drugs such as classical antiepileptic drugs and anesthetics (high-dose midazolam, propofol, and barbiturates). Most of the time, this polytherapy has a severe impact on several key functions (e.g. severe hypotension with thiopental which can reduce brain perfusion, cardiotoxicity with pheno- or pentobarbital, or the propofol infusion syndrome). A new terminology has recently been introduced following the London-Innsbruck Colloquium on SE held in Oxford in April 2011: super-refractory status epilepticus (SRSE). It is defined as continuous or recurrent seizures lasting 24 h or more following initiation of the previously mentioned anesthetic protocols, including cases in which seizure control is attained after induction of anesthetic drugs but recurs on weaning the patient off the anesthetic agent [6]. For management of RSE/SRSE, we are far from the standards of evidenced-based medicine owing to the lack of controlled, randomized blinded clinical trials [2,7].

According to the current definitions, SE should be considered a rare disease (in Europe if affecting less than 50/100,000, in the USA if affecting fewer than 200,000 Americans at any given time, indeed the case following some estimate of 150,000 cases of SE in the USA). RSE and SRSE are even rarer. An estimate in the USA brought 13/100,000 for SRSE [8]. The difficulty to obtain an informed consent and the unfavorable cost/benefits ratio for a pharmaceutical company are hurdles but the risk of cancellation of the clinical trial owing to a low recruitment is probably the main reason that explains why it is so difficult to obtain enough clinical data on the success of treatment strategies. A given trial ought to be multicenter and possibly international, introducing additional funding and regulatory challenges. The established status epilepticus treatment trial was, for instance, discussed in 2009, first mentioned in a publication in 2011, planned to be starting recruiting in 2012 but only registered in the clinical trial database end of 2013 and after 3 years was still recruiting patients.

Although the basis for refractoriness is not exactly known, several hypothesis are considered; some linked to pharmacokinetics (role of p-glycoprotein transport molecules that are upregulated) or to pharmacodynamics (changes in glutamate receptor density and/or receptor subunit composition, internalization/down-regulation and subunit changes of Gamma-AminoButyric Acid A receptors, neuroinflammation, etc.). Do we have then a molecule that potentially acts on several of these targets? The answer is definitely yes.

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Ketamine is a noncompetitive antagonist of the *N*-methyl-D-aspartate (NMDA) glutamate receptor that has several mechanisms of action including an effect on (neuro)inflammation [5,9]. It is still the only NMDA antagonist licensed as an injectable drug in different countries and remains an anesthetic of choice in some difficult field conditions. In 2012, for the 50th anniversary of the discovery of ketamine, a special issue of CNS Neurosciences and Therapeutics covered the vast range of effects and clinical applications of ketamine. One of the topic considered was the use of ketamine for the treatment of RSE [5]. SE can also be caused by poisoning by the deadly organophosphorus nerve agents, chemical warfare agents that have been part of military arsenals during the Cold War and used in terrorist attacks in the past in Japan (1994 and 1995) or more recently in the war in Syria. Interestingly, ketamine, in combination with atropine and a benzodiazepine, appears a good candidate for the out-of-hospital treatment of severe nerve agent-induced SE [10]. The ketamine/atropine combination also exhibited beneficial therapeutic effects in intoxicated rats such as a limitation of convulsion-induced hyperthermia [11]. At the time the 2013 review was published [5], it was clear that more and more clinicians were advocating that ketamine should be considered earlier in the management of RSE. But 4 years after, has the situation evolved in the specific field of SE/RSE/SRSE? Unfortunately, the answer is no and the medical community seems still largely reluctant to use ketamine. One of the reasons is that ketamine rarely appears in the management algorithms. Hence, many clinicians are not even aware of the properties of the molecule! In their recent small survey in Canada, Zeiler and West [12] reported that less than half the respondents knew the literature on the effect of ketamine on seizures. Moreover, some clinicians heavily stress on the side effects or possible deleterious effects of ketamine (cited in [5] for instance), some being either not relevant when treating a life-threatening condition (bad dreams) or not substantiated by the recent studies (increase in intracranial pressure for instance [13]). Compared to the anesthetics used in the treatment of SRSE, ketamine has less negative cardiovascular impact and does not easily induce respiratory failure. Since the publication of this 2013 review [5], another review [14] and some retrospective studies were published showing ketamine as a relatively effective and safe drug for RSE [15–17]. However, because it is still used very late in the management of SE (e.g. introduction after a median time of 3 [17] or 9 days of SE [15]) with very variable protocols, it is very difficult to draw firm conclusions. Earlier administration is probably a key to success [12,18], at least by limiting the uncontrolled adverse effects and interactions related to polypharmacy. Concerns about possible developmental neurotoxicity might limit its pediatric use although reports suggest its benefits, notably by avoiding endotracheal intubation, a negative prognostic factor of morbidity and mortality [19]. For the reasons mentioned before, we are still missing randomized controlled clinical trials. Hopefully, the 'ketamine in RSE' multicenter clinical trial initiated last year by the Meyer children's hospital in Italy for children up to 18 years of age will bring valuable results ([20], NCT02431663 in clinicaltrials.gov). The medical community should also make up its mind from well-conducted preclinical studies performed on appropriate models.

Future directions could then be to:

- increase the pathophysiological understanding of SE/RSE/SRSE using relevant experimental models;
- improve the preclinical knowledge on the efficacy of ketamine, alone or more importantly in combination, on the reasons why it may lose its efficacy and on the key parameters that may be linked to success (brain concentration?) [5];
- win the battle of perceptions and fight against the false and deeply mind-rooted ideas (e.g. contraindication of ketamine in neurological cases);
- increase information of the medical community about the usefulness of ketamine so they may consider using it for RSE/SRSE early enough to get the benefits [12];
- make readily available the more efficient S(+) ketamine in countries where it is not yet licensed;
- finally, given the social and economical impact of SE/RSE/SRSE [8], use the rules that are in effect for rare diseases in designing and accepting clinical trials.

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Declaration of interest

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