“Prevention of Sudden Unexpected Death in Epilepsy: A realistic goal?”

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An synopsis made by Ruben de Haan

What is SUDEP?

Sudden Death in Epilepsy (SUDEP) is the term for a unexpected death as result of a epileptic seizure.

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EPIDEMIOLOGY AND CLINICAL ASPECTS OF PHARMACORESISTANCE

Prevention of sudden unexpected death in epilepsy: A realistic goal?

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Summary

Sudden unexpected death in epilepsy (SUDEP) represents one of the most severe consequences of drug-resistant epilepsy, for which no evidence-based prevention is available. Development of effective prevention will depend on the following: (1) better understanding of the pathophysiology of SUDEP to define the most appropriate targets of intervention, and (2) identification of risk factors for SUDEP that would allow for the design of feasible clinical trials to test targeted interventions in high-risk populations. The most important known risk factor is the occurrence and frequency of generalized tonic–clonic seizure (GTCS), a seizure type that triggers the majority of witnessed SUDEP. Therefore, one likely way to prevent SUDEP is to minimize the risk of GTCS with optimal medical management and patient education. However, whether one might prevent SUDEP in patients with refractory epilepsy by using more frequent review of antiepileptic treatment and earlier referral for presurgical evaluation, remains to be seen. Another hypothetical strategy to prevent SUDEP is to reduce the risk of GTCS-induced postictal respiratory distress. This might be achieved by using lattice pillow, providing nocturnal supervision, reinforcing interictal serotoninergic tone, and lowering opiate- or adenosine-induced postictal brainstem depression. Promising interventions can be tested first on surrogate markers, such as postictal hypoxia in epilepsy monitoring units (EMUs), before SUDEP trials can be implemented. EMU safety should also be improved to avoid SUDEP occurrence in that setting. Finally, the development of ambulatory SUDEP prevention devices should be encouraged but raises a number of unsolved issues.

KEY WORDS: Epilepsy, Seizure, Death, Sudden unexpected death in epilepsy, Prevention.

Sudden unexpected death in epilepsy (SUDEP) represents the main epilepsy-related cause of death, with high life-time prevalence in patients with uncontrolled seizure (Shorvon & Tomson, 2011). Indeed, >20% of patients with childhood-onset epilepsy who fail to achieve long-term seizure freedom will die of SUDEP within 40 years of follow-up (Sillanpaa & Shinnar, 2010). These figures, together with the devastating impact of the sudden loss of young adults, should make prevention of SUDEP a priority for the epilepsy community. So far, however, we lack evidence for the effectiveness of any intervention aimed at preventing SUDEP. The development of effective interventions is hampered by our incomplete understanding of the pathophysiology of SUDEP. It is therefore important to first consider the current state of knowledge of the mechanisms leading to SUDEP before exploring the most relevant directions which could lead to realistic and timely progress in SUDEP prevention.

Targeting the Appropriate Patients for Future Clinical Trials

The highest SUDEP incidence has so far been reported in patients undergoing presurgical evaluation or having failed epilepsy surgery, with rates up to 9.3/1,000 patient-year (Dasheiff, 1991). According to this highest but possibly overestimated figure (other studies have reported lower rates around 6/1,000 patient-years in comparable

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populations; Nilsson et al., 2003), to demonstrate that a 6-month–duration intervention reduces the incidence of SUDEP by 50% will require a sample size of about 12,000 patients. Such studies raise obvious major feasibility issues. Two alternative approaches may be considered. The first is to establish if there is a clear relationship in epidemiologic studies between SUDEP and other adverse consequences of seizures, such as serious injuries or emergency department attendances and thus provide surrogate end points and increased power. The second is to apply simple population-based interventions in well-defined communities with prerexisting validated SUDEP registers.

Knowledge of SUDEP risk factors has recently advanced thanks to the pooled analysis of four major case–control studies performed by the Subcommission on Mortality of the ILAE Commission on Epidemiology (Hesdorffer et al., 2011, 2012). As previously suggested, the presence and frequency of generalized tonic–clonic seizures (GTCS; either primary or secondary generalized) was found to represent the main risk factor, with an odds ratio of >15 for patients with three or more GTCS per month (Hesdorffer et al., 2012). A few other risk factors proved significant, but with odds ratios <2, including male gender, age of onset of epilepsy <16 years, duration of epilepsy >15 years, and polytherapy (Hesdorffer et al., 2011). However, when adjustments were made for the number of GTCS, neither polytherapy nor the use of specific antiepileptic drugs (AEDs) such as lamotrigine or carbamazepine, was associated with an increased risk of SUDEP (Hesdorffer et al., 2012).

How these figures translate into incidence of SUDEP in specific populations remains unknown. In the pooled analysis discussed above, cases and controls were mixed populations of patients seen at epilepsy centers and community-based cohorts of prevalent epilepsy (Hesdorffer et al., 2011), both of which demonstrate comparable SUDEP rates between 1 and 2/1,000 patient-years (Shorvon & Tomson, 2011). About 12% of the controls had more than three GTCS per year (Hesdorffer et al., 2011). Extrapolating from the data reported in this analysis, one would suspect that the subgroup of patients with ≥ 3 GTCS/year would have an annual rate of SUDEP grossly ranging from 5 to 18/1,000 patient-years, thus raising the same feasibility issue for clinical trials as described above for patients with surgical failure.

Therefore, we still need to characterize populations with greater risk of SUDEP to test the impact of potentially preventive interventions. This will require further epidemiologic studies in well-selected and phenotyped populations combining previously identified predictors (nonidiopathic refractory epilepsy with an early age of onset affecting young adults with frequent GTCS), coupled with the identification of novel and independent risk factors that could more directly reflect the pathophysiology of SUDEP (nocturnal seizures, prolonged postictal electroencephalography [EEG] suppression, ictal/postictal hypoxemia, depression, and/or other biomarkers of serotoninergic dysfunction, and so on). Such studies should be a priority in the field.

Targeting the Mechanisms Leading to SUDEP

A better understanding of SUDEP pathophysiology should help identify mechanisms to be targeted by preventive interventions, as well as patients with sufficiently high SUDEP risk to allow feasible clinical trials. While still debated, the mechanisms leading to SUDEP seem to be usually triggered by a GTCS (Langan et al., 2000; Tomson et al., 2008). Exceptions, for which monitored evidence is lacking, might include rare channelopathies responsible for both epilepsy and cardiac predisposition to sudden death, or non–seizure-related arrhythmic sudden cardiac deaths, and from partial seizures triggering ictal malignant arrhythmias. In the rare patients with a known mutation of *SCN5A* or *KCNH2* genes or family history of *SCN1A* mutation who died of SUDEP, information regarding the circumstances of death was either lacking or suggested that patients died in bed unwitnessed or after a convulsion (Hindocha et al., 2008; Aurlien et al., 2009; Tu et al., 2011). The only reported malignant arrhythmia triggered by a partial seizure and which did not spontaneously resolve, was a successfully resuscitated near-SUDEP (Espinosa et al., 2009). In fact, ictal asystole, hitherto considered a potential cause of SUDEP, is now believed by many to be generally a self-limiting process, whereby secondary brain hypoxia aborts the ictal discharge and its related central neurovegetative dysfunction, leading to restoration of normal cardiac activity (Schuele et al., 2010).

Following GTCS, the pattern observed in the rare monitored cases of SUDEP typically combines severe postictal EEG suppression, which does not recover until death, hypopnea and irregular breathing followed by apnea, and electrocardiography (ECG) abnormalities including bradycardia and terminal asystole (Nashef & Ryvlin, 2009). A number of issues, however, remain unanswered: (1) does the severity of immediate postictal EEG suppression differ between SUDEP and following GTCS in general? what is the contribution of brain hypoxia to the occurrence and persistence of EEG flattening? (2) how adequate is the often observed postictal respiratory effort preceding apnea? and if not, what are the primary mechanism(s) contributing to impaired ventilation (hypoventilation with ineffective irregular respiratory muscle contraction, neurogenic pulmonary edema, obstructive apnea promoted by upper airway muscle hypotonia and the prone position)? (3) similarly, how good is cardiac output during periods of altered cardiac rhythm and abnormal QRS complex observed before terminal asystole?

Based on available information, including those collected within MORTEMUS (MORTality in Epilepsy Monitoring Unit Study), one can speculate on the most likely mechanisms of SUDEP. Apnea is already present during GTCS, and might be responsible for significant hypoxemia in some cases, contributed to by ventilation-perfusion inequality (Bateman et al., 2008; Seyal et al., 2010). A GTCS-induced release of endogenous opioids and adenosine within the brain and brainstem, believed to be instrumental in seizure termination, may then be responsible for postictal EEG suppression and central neurovegetative dysfunction translating into both respiratory and cardiac abnormalities. Respiratory abnormalities, which might be aggravated by the prone position, will include central hypopnea and apnea, neurogenic pulmonary edema, impaired gas transfer, as well as upper airways hypotonia, all of which might worsen brainstem hypoxia and associated cardiorespiratory failure. This vicious cycle is likely to be further aggravated by cerebral hypoperfusion secondary to bradycardia and transient asystole. Terminal asystole is usually observed after terminal apnea. Therefore, the three main contributing and interrelated factors, that is, cardiac, respiratory, and brainstem dysfunctions, appear both entangled and reciprocally aggravating. This might account for the variations observed in the duration and sequence of events leading to SUDEP in monitored patients.

Overall, rather than depending on one single or primary factor, SUDEP in most cases appears likely to result from a GTCS-induced global and multifactorial neurovegetative breakdown. Prevention might in turn target a number of contributing factors, with the aims of: (1) reducing the occurrence of GTCS with optimal treatment), (2) detecting postictal cardiorespiratory distress (seizure, SpO_2, ECG monitor), (3) reducing the risk of upper airways partial obstruction and postictal respiratory distress (lattice pillow, supervision, O_2), (4) reducing central hypoventilation through physical stimulation, (5) reducing endogenous opioid and/or adenosine mediated postictal brain and brainstem depression, and (6) reinforcing serotonin-related respiratory rescue mechanisms (SSRI).

Potential Interventions for Preventing SUDEP

More appropriate and more effective antiepileptic treatment

The strong epidemiologic and pathophysiologic link between seizures, and more specifically GTCS, and SUDEP, suggests that efforts to minimize the risk of seizures should translate into lower rate of SUDEP. A number of general recommendations for optimizing epilepsy therapy deserve to be emphasized in this context, including:

1 *Optimal choice of AED regimen*, based on an accurate diagnosis of the epilepsy syndrome to avoid on the one hand, undiagnosed and untreated active epilepsy, and on the other hand, misclassified and mistreated idiopathic generalized epilepsy using aggravating narrow spectrum AEDs. A further and controversial issue is if specific monotherapies or polytherapy can carry an increased SUDEP risk. Regarding monotherapy, a few reports have suggested that lamotrigine and carbamazepine could be associated with a higher risk of SUDEP (Timmings, 1993; Langan et al., 2005; Aurlien et al., 2010). However, these findings were not confirmed by the pooled analysis of case–controlled studies discussed above (Hesdorffer et al., 2012). This analysis also demonstrated that the previously reported association between polytherapy and risk of SUDEP reflected higher frequency of GTCS in patients with greater number of AEDs, and vanished after adjusting for seizure frequency (Hesdorffer et al., 2012). In fact, a meta-analysis of all double-blind randomized placebo controlled trials performed in adult patients with refractory epilepsy showed that patients receiving an add-on AED had a sevenfold lower risk of SUDEP (0.9/1,000 patient-years) than those receiving placebo on top of their baseline AED treatment (6.9/1,000 patient-years; Ryvlin et al., 2011). Although these findings cannot readily translate into clinical recommendations, they suggest that review of treatment in patients with refractory epilepsy might have a beneficial impact on the risk of SUDEP.

2 *Patients' education* to promote adherence to treatment, avoidance of seizure triggering factors (lack of sleep, alcohol, medications lowering seizure threshold, abrupt AED changes), and appropriate reaction to seizure clusters (rescue medication), missed medication (redosing), or to any other situations that could lower AEDs levels (gastrointestinal disorders, pregnancy, or prescription of other drugs such as oral contraceptive in patients treated with lamotrigine; (Devinsky, 2012).

3 *Timely referral to presurgical evaluation*, with the view that successful curative treatment should offer the most effective protection against SUDEP. Although this conclusion is supported by studies showing higher risk of SUDEP in patients who failed surgery as compared to those who achieved seizure freedom (Sperling et al., 1999; Salanova et al., 2002; Sperling et al., 2005), we still lack definite proof that this difference primarily reflects the impact of epilepsy surgery, rather than preexisting biologic differences between the two groups (Ryvlin et al., 2006). For instance, patients failing temporal lobe surgery might have epilepsy involving extratemporal brain regions controlling cardiorespiratory functions, leading to increased risk of SUDEP (Ryvlin & Kahane, 2003). This hypothesis supports improving the delineation and surgical management of patients whose epileptogenic zone could represent a risk factor for SUDEP, such as the insular cortex (Ryvlin, 2006).

Reducing the risk of postictal respiratory failure

1 *Lattice pillows* have been proposed to reduce the contribution of the prone position to postictal respiratory distress and thus SUDEP (Devinsky, 2012). Although having the face down in the pillow might not necessarily result in major airways obstruction, the observation that more SUDEP patients are found prone than expected by chance, with 71% found prone in one study (Kloster & Engelskjøn, 1999), suggests that this environmental factor plays a significant role, in as much as patients in postictal coma are unable to correct their position in response to hypoxemia (Nashef et al., 1998). The impact of sleep position upon the risk of sudden infant death syndrome also emphasizes the potential role of such intervention. However, no study has evaluated the benefit of using lattice pillows in epilepsy. It would be worth comparing the impact of using lattice, standard, and no pillow upon ictal/postictal SpO_2 measurements in an epilepsy monitoring unit (EMU) setting.

2 *Nocturnal supervision* was found to be protective of SUDEP in one case–control study (Langan et al., 2005), a finding supported by another observational study (Nashef et al., 1995). The development of seizure-detecting devices enable more effective night time supervision, but also raises the issue of false-positive/false-negative detection rates as well as that of the risk/benefit balance of such intervention on patients' quality of life. The decision to apply such measures needs to be individualized according to patient preference, seizure profile (nocturnal, generalized, frequency), and overall risk of SUDEP, with the knowledge that seizure-detecting devices have not been demonstrated to reduce the risk of SUDEP. Although most SUDEP cases are unwitnessed, one must also be aware that the intervention of a witness does not necessarily preclude the occurrence of SUDEP, as illustrated by video recording of patients who died in the EMU while being supervised. Turning the patient from prone to recovery position during the early postictal phase might be sufficient to reverse respiratory distress in some cases, but more active resuscitation procedures are likely to be needed in others. Therefore, families aiming at organizing nocturnal supervision for a relative at significant risk of SUDEP should be educated in order to react promptly and efficiently to ictal/postictal cardiorespiratory distress.

3 *Supervision in EMUs* raises similar issues, despite the fact that SUDEP in EMUs are extremely rare and its contribution to all SUDEPs in society is minimal. Nevertheless, one could rightly consider that such events should not occur at all in a dedicated medical environment with staff supposedly trained to anticipate the consequences of seizures and GTCS, particularly that the latter are often promoted by tapering AEDs. Therefore, physicians and nurses face clear-cut responsibilities in managing SUDEP prevention in EMUs. The MORTEMUS study points to major weaknesses in the general organization of EMU safety with often inadequate supervision, especially at night. Observations from MORTEMUS support the development of safety guidelines in EMUs, with two priorities: (1) systematic monitoring of ECG and SpO_2 with appropriate alarm system in all patients undergoing long-term video-EEG monitoring, (2) organization of specific emergency code in EMUs, (3) education of EMU staff to quickly identify ictal/postictal cardiorespiratory distress and start appropriate cardiopulmonary resuscitation.

4 *Postictal O_2 therapy* is being used systematically in some EMUs, without any evidence that this procedure reduces the risk of postictal respiratory distress or SUDEP. However, in a mice model of seizure-induced SUDEP, O_2 therapy proved extremely efficacious to prevent death (Venit et al., 2004). Although it remains difficult to extrapolate such experimental findings to humans, it appears reasonable to provide O_2 therapy in patients with postictal decreased SpO_2 or respiratory distress. Studies are also warranted of the impact of postictal O_2 therapy on various outcomes, including the duration of postictal EEG suppression and clinical state.

5 *Serotoninergic drug*, including selective serotonin reuptake inhibitor (SSRI), might offer a way to decrease the risk of postictal central apnea. Lower brainstem serotoninergic nuclei play an important role in the regulation of respiration (Richter et al., 2003), in particular when recurrent hypoxia leads to a specific plasticity phenomenon called long-term facilitation (Ling et al., 2001; Mahamed & Mitchell, 2008). Abnormalities of brainstem serotoninergic nuclei have been described in sudden infant death syndrome (SIDS) (Paterson et al., 2006), as well as in mice models of SUDEP (Uteshev et al., 2010; Faingold et al., 2011a). Accordingly, fluoxetine was shown to prevent the occurrence of fatal apnea in these models (Tupal & Faingold, 2006; Faingold et al., 2011b). These experimental data prompted a retrospective study looking at the association between SSRI treatment and pulse oximetry in patients undergoing video-EEG monitoring (Bateman et al., 2010). Ictal/postictal hypoxemia was significantly less frequent in patients receiving SSRI than in those without such treatment (Bateman et al., 2010). Two double-blind randomized placebo-controlled trials are underway to confirm this finding, but whatever the outcome, the relevance for SUDEP prevention remains to be shown.

6 *Inhibitors of opiate and adenosine receptors* might also contribute, thereby reducing the severity of postictal EEG and neurovegetative dysfunction (Shen et al., 2010). However, this therapeutic strategy carries the risk of aggravating the duration, frequency or severity of seizures, as illustrated by the proconvulsant effect of caffeine, a potent antagonist of adenosine receptors (Shapira et al., 1985). Conversely, naltrexone, an opioid receptor antagonist, is used long term in patients with addiction (Tiihonen et al., 2012), without a known effect on

Synopsis:

The report starts with the quote that more than 20% of the patients that had epileptic seizures since their birth die within 40 years.
A lot of context and reasoning (as the name suggests) concerning SUDEP is still unclear which makes targetting patients and prevention difficult.
The best way to provide a solution to SUDEP is to focus research on patients with known risk-factors which include noctural seizures, depression and hypoxemia (low level of oxygen in blood).
Untill then the following measures could help assist in lowering the chance on fatal seizuring:

1. Reduce amount of seizures by AED (Antiepileptic Drugs)
2. Detect cardiac distress (EEG scan)
3. Keep airways free

End of synopsis.