Current Literature

In Clinical Science



SUDEP: Sudden Unexpected Death in Epilepsy on Placebo?

Risk of Sudden Unexpected Death in Epilepsy in Patients Given Adjunctive Antiepileptic Treatment for Refractory Seizures: A Meta-Analysis of Placebo-Controlled Randomised Trials.

Philippe Ryvlin, Michel Cucherat, Sylvain Rheims. Lancet Neurol 2011;10:961–968.

BACKGROUND: Sudden unexpected death in epilepsy (SUDEP) represents the main cause of death in patients with refractory epilepsy. No evidence-based intervention to prevent SUDEP exists. We postulated that pooling data from randomised placebo-controlled trials in patients with refractory epilepsy might show a lower incidence of SUDEP in patients receiving antiepileptic drugs (AEDs) at efficacious doses than in those receiving placebo. METHODS: We searched Medline and the Cochrane Library for randomised trials investigating any AED in the add-on treatment of drug-resistant epilepsy in adults. We extracted the number and causes of death in patients allocated to AEDs at doses that were more efficacious than placebo against seizures, AEDs at non-efficacious doses, and placebo. In our primary analysis, we compared the occurrence of definite or probable SUDEP between patients given efficacious AED doses and those given placebo using the Mantel-Haenszel method, with exclusion of trials with no event. FINDINGS: Data of 33 deaths, including 20 deemed as SUDEP, were extracted from 112 eligible randomised trials. 18 deaths were classified as definite or probable SUDEP and two as possible SUDEP. Definite or probable SUDEP, all SUDEP, and all causes of death were significantly less frequent in the efficacious AED group than in the placebo group, with odds ratios of 0.17 (95% CI 0·05–0·57, p=0·0046), 0·17 (0·05–0·57, p=0·0046), and 0·37 (0·17–0·81, p=0·0131), respectively. Rates of definite or probable SUDEP per 1000 person-years were 0.9 (95% CI 0.2-2.7) in patients who received efficacious AED doses and 6.9 (3.8–11.6) in those allocated to placebo. INTERPRETATION: Treatment with adjunctive AEDs at efficacious doses may have reduced the incidence of definite or probable SUDEP by more than seven times compared with placebo in patients with previously uncontrolled seizures. This result provides evidence in favour of active treatment revision for patients with refractory epilepsy.

Commentary

Sudden unexpected death in epilepsy (SUDEP) has in recent years been better characterized and increasingly discussed. SUDEP is defined as "sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in a patient with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus" (1). SUDEP is most convincingly established ("definite SUDEP") by postmortem examination to exclude other causes of death. Probable SUDEP can be established if all criteria for SUDEP are met but postmortem examination is not available, and the term "possible SUDEP" is applied when SUDEP is strongly suspected but evidence to convincingly exclude competing causes of death is lacking. A single mechanism is not established, but pulmonary, cardiac, and autonomic causes have all been implicated.

Several risk factors for SUDEP have been identified. These include frequent seizures—particularly generalized tonic-clonic seizures—subtherapeutic antiepileptic drug (AED) levels, frequent AED changes, AED polytherapy, long dura-

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tion of epilepsy, and developmental delay. Young adults are frequently affected.

Despite an improved understanding of risk factors and underlying mechanisms, relatively less progress has been made in defining interventions that reduce the risk of SUDEP. Various means of monitoring for seizures, particularly during the night (e.g., bed alarms, respiratory or cardiac monitoring), have been proposed. Training of family members and caregivers in cardiopulmonary resuscitation (CPR) is recommended. Given the association of SUDEP with a proximate seizure, risk reduction might be most directly addressed by improving seizure control, but data are limited on the benefits of specific interventions. Reduction in mortality, including SUDEP, from successful epilepsy surgery has been observed (2, 3).

Understanding the optimal management of antiepileptic medication in patients at risk for SUDEP has been particularly vexing. Clearly, improved seizure control should be a goal; however, AED polytherapy is associated with a higher risk of SUDEP. Is the latter finding simply a marker for more severe epilepsy, or are there inherent risks of multidrug therapy?

The current work by Ryvlin, Cucherat, and Rheims opens a new window into some of these issues by examining the fate of some 21,224 patients enrolled in 112 randomized controlled trials of 27 AEDs over 5,589 patient-years. This approach har-

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nesses the power of large numbers of patients to study the incidence of low frequency events (SUDEP) over relatively short periods of time (the duration of a typical AED clinical trial). Fourteen of these trials contained 20 SUDEP patients (11 definite, 7 probable, 2 possible). The primary endpoint of the study was to compare the incidence of definite and probable SUDEP in patients receiving AEDs at efficacious doses with those randomized to placebo. Secondary analyses included patients with possible SUDEP, all deaths, and examined incidence in specific subgroups based on epilepsy syndrome or AED.

The results were striking: randomization to AED at efficacious doses was associated with reduced odds of SUDEP (odds ratio [OR] 0.17; confidence interval [CI] 0.05–0.57; p = 0.0046). The overall incidence of definite or probable SUDEP in patients on efficacious AED doses (0.9/1,000 patient-years) contrasted starkly with the higher incidence (6.9/1,000 patient-years) in those randomized to placebo. There was no similar reduction in the risk of non-SUDEP deaths. Subgroup analyses were largely unrevealing, probably because of relatively small numbers, though all SUDEP occurred in patients enrolled in studies of partial seizures. Data on seizure frequency in the patients with SUDEP were not presented. Reduced seizure frequency in the active treatment group is the most probable mechanism to explain the group differences; it is difficult to account for these differences by any means other than improved seizure control. Patients are more intensively monitored during a clinical trial, but this should apply equally to the active treatment and placebo groups in double-blinded trials.

These are the most convincing findings to date about the effects of medical interventions on SUDEP risk. They convincingly demonstrate that, at least in the short term, a medication intervention can reduce the risk of SUDEP. The data strongly suggest that efforts to improve seizure control should be paramount and that polytherapy per se did not increase the risk of SUDEP.

What does this mean for the design of future clinical trials? Concern about placebo use in epilepsy trials has been focused on the use of placebo or "active controls"—presumed subtherapeutic doses of AEDs—in monotherapy trials. A proposal to use historical control data rather than placebo groups in these studies has been accepted by the FDA, and the first study using this design has just been reported (4, 5). Add-on therapy trials in epilepsy have generated less concern, because something approaching clinical equipoise has been assumed—the patient may be randomized to placebo, but this is short term. They remain on what has presumably

been the most effective medical therapy available to date, the risks of the active drug are still not fully known, and they will typically have access to the new drug at the end of the short blinded phase. Perhaps some of these assumptions should be reconsidered. Certainly a minimum goal should be to shorten the placebo phase of studies as much as possible. The practice of reducing polytherapy so that a patient might qualify for a clinical trial—including possibly randomization to the placebo arm—may not be wise. Perhaps a discussion of SUDEP should be part of the enrollment process in clinical trials.

We must be cautious in applying lessons from this single retrospective study. There are potential statistical issues with meta-analysis in the setting of low frequency events and many "zero-event" studies in which SUDEP did not occur. It is possible that the benefits of adjunctive medication may wane over time (the ending of the "honeymoon period"). Patients may have difficulty tolerating intensive polytherapy outside of the confines of a brief controlled study.

Nonetheless, these findings argue for the benefits of improved seizure control on SUDEP risk and are reassuring regarding polytherapy and SUDEP risk. The magnitude of the effect in this study is difficult to ignore. Some healthcare providers have developed a sort of therapeutic nihilism regarding polytherapy trials because existing data suggest that few additional refractory epilepsy patients are rendered seizure-free by these efforts. However, every change that reduces medication side effects or reduces seizure frequency is an incremental gain, and perhaps, considering the current study, might also have an effect on the risk of SUDEP. Further efforts to better understand how to mitigate the risk of SUDEP are needed.

by David C. Spencer, MD

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