Falling Status Epilepticus mortality rates in England & Wales: 2001-2013?

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Status Epilepticus (SE) is associated with significant mortality and accounts for ~10% of epilepsy-related deaths. Epilepsy and SE mortality data from 2001 to 2013, in addition to annual age group populations for England and Wales, were obtained from the Office of National Statistics website (www.ons.gov.uk). Age-adjusted mortality rates for epilepsy and SE with 95% Confidence Intervals (CI) were calculated using the European Standard Population. Trends in mortality rates of both Epilepsy and SE were investigated using the Spearman coefficient. The crude mean Epilepsy mortality rate per 100,000 person years between 2001 and 2013 was 1.87 (95% CI 1.83, 1.91) with a corresponding SE mortality rate of 0.14 (95% CI 0.13, 0.15). The mean age-adjusted Epilepsy mortality rate per 100000 person years was 3.24 (95% CI 3.12, 3.35) with a corresponding SE mortality rate of 0.24 (95% CI 0.21, 0.27). All Epilepsy deaths significantly decreased from 2001 to 2013 (Spearman's Rho -0.733, $p=0.004$); this decrease was predominantly due to a decrease in SE deaths (Spearman's Rho -0.917, $p<0.001$). In summary our finding supports the hypothesis that the policy of early and aggressive treatment of SE may be improving the prognosis of this condition in England and Wales.

Status epilepticus (SE) has a high mortality rate (10-20%), accounting for ~10% of epilepsy-related deaths[1]. SE has traditionally been defined as a seizure lasting 30 minutes or more, but treatment at this stage may be too late to prevent serious consequences (this has resulted in a proposal to change the definition of SE)[2].

A major advance in the last two decades has been the proposal, first advocated by Lowenstein and colleagues in 1999, that prolonged convulsive seizures (>5 minutes) be considered as "operational" SE with prompt , more aggressive treatment[3]. The need for two dimensions is recognised in the recent ILAE definition and classification of SE, which defines two time points: t_1, - the operational definition of SE (the time point at which a seizure should be regarded as an *"abnormally prolonged seizure"*) and t_2 – the traditional definition of SE (the time of on-going seizure activity beyond which there is a risk of long-term consequences)[4].

We wished to determine if this drive to earlier, more aggressive treatment has been associated with a change in SE mortality in England and Wales.

Methods

Epilepsy mortality data and annual age group populations for England and Wales were obtained from the Office of National Statistics website (www.ons.gov.uk). Prior to 2001, mortality rates were classified using the WHO ICD-9 classification, with the WHO ICD-10 classification employed thereafter. Consequently direct comparison of mortality rates pre- and post-2001 was not felt to be feasible. The majority of epilepsy deaths were classified as "epilepsy (not otherwise specified)", which may include some deaths due to SE, consequently underestimating SE mortality. There is however no reason to believe that this rate of misclassification would differ from year to year[5].

Age-adjusted mortality rates for epilepsy and SE with 95% Confidence Intervals (CI) were calculated using the European Standard Population (first introduced in 1976), using the Office of National Statistics guidelines[6].(see eTable1).We used the Spearman coefficient to measure trends in mortality rates of both epilepsy and SE. Statistics were calculated using SPSS v22. A p-value <0.05 was considered statistically significant.

Results

The number of annual deaths attributable to epilepsy was relatively stable with a mean annual total of 1021 deaths (95% CI 1000, 1042), with a corresponding annual mean of 77 deaths (95% C.I. 70, 83) attributable to SE, accounting for 7.5% (95% CI 6.8, 8.2) of the deaths attributable to epilepsy over the 13 years. The crude mean epilepsy mortality rate per 100,000 person years between 2001 and 2013 was 1.87 (95% CI 1.83, 1.91) with an SE rate of 0.14 (95% CI 0.13, 0.15) (Table 1). The mean age-adjusted epilepsy mortality rate per 100,000 person years was 3.24 (95% CI 3.12, 3.35) with a corresponding SE mortality rate of 0.24 (95% CI 0.21, 0.27). There was a significant trend towards reduced mortality for all age-adjusted epilepsy deaths between 2001 and 2013 (Spearman's Rho -0.733, p=0.004) that was mainly accounted for by a reduction in age-adjusted SE deaths (Spearman's Rho -0.917, p<0.001) rather than non-SE epilepsy deaths (Spearman's Rho -0.544, p=0.055). Indeed, the temporal trends for SE and non-SE deaths diverge over that period (Figure 1).

Discussion

We examined epilepsy- and SE-related mortality rates in England & Wales between 2001 & 2013. Whereas the overall total annual deaths attributable to epilepsy remained relatively stable, despite a population increase of 4,588,251, the annual number of SE-related deaths is falling (as evidenced by the significant trend for unadjusted SE mortality rates). More

encouragingly, the age adjusted mortality rates for both SE and all epilepsy deaths are decreasing. Whilst it would be informative to know at what time point an operational diagnosis of SE was adopted, the data do not allow for such precision. The expectation is however that any change would have been gradual, as is mirrored by the gradual incorporation of an operational diagnosis of SE into the proposed treatment protocols of SE of professional bodies such as those of the EFNS (2010)[7] and the Neurocritical Care Society (2012)[8].

There is a paucity of data regarding temporal trends in SE mortality, with this being the first such report from the United Kingdom; the only previous significant SE study from the UK was the North London Convulsive Status Epilepticus in Childhood Surveillance Study (NLCSECSS)[9]. Previous mortality SE estimates have come from seven population based SE studies (and single institution cohort studies)[1], only one of which was carried out over several years (so allowing for an examination of SE mortality trends). In this study the incidence and case fatality (CF) for generalised convulsive SE in the state of California (1991-1998) were calculated using a state-wide database of all people with a hospital diagnosis of SE[10]. The overall case fatality was 10.7%, but with a much lower rate of 3.5% for those admitted with a primary diagnosis of generalised convulsive SE. Whilst the overall mortality for SE remained stable over the period of observation, the mortality of those admitted with a primary diagnosis of SE decreased from 4.7% to 3.2%. At the same time the annual incidence of SE decreased by 42% between 1991 and 1998 from 8.5 to 4.9/100,000 ($p<0.001$), possibly suggesting more efficient and aggressive treatment of out-of-hospital prolonged seizures and SE.[10]

Two more recent studies have looked at trends in SE-related hospital admissions and mortality in the United States, using representative samples of hospitals from national databases.[11 12] In one study, data from the US National Hospital Discharge Survey were used to identify hospital discharges with SE between 1979 and 2010.[11] In total 760,117 discharges with SE were identified over the 32 years. In that time the incidence of SE

increased from 3.5/100,000/year in 1979 to 12.5/100,000/year in 2010, representing an overall increase of 12.5% per year, with the most significant increase occurring between 1979 and 1991 (17.7% annual increase). There was a subsequent decrease in the incidence of SE in the 1990s before a further increase in the 2000s. The corresponding cumulative in-hospital mortality was 9.2% (95% CI 9.1,9.2) with no significant observed variation over the 32 years.

The second study utilised the Healthcare Cost and Utilisation Project Nationwide Inpatient Sample data to identify SE hospital admissions and SE-associated mortality between 1999 and 2010.[12] When considered as the primary cause of death, the age-adjusted mortality rate for SE increased by 5.6% between 1999 and 2010 from 0.179/100,000 to 0.189/100,000, with a corresponding increase of 56.4% in age-standardised SE hospital admissions from 8.86/100000 in 1999 to 13.86/100,000 in 2010.[9] All three US studies used the WHO ICD-9 coding system.

In comparing the three US studies and our findings several observations can be made. Whilst the earlier California study[10] was confined to admissions with generalised convulsive SE, the later studies[11,12] included all cases of SE. Greater recognition of subtle cases of SE and non-convulsive SE, particularly in the ICU setting with the greater availability of ambulatory EEG, is likely to be a significant factor in the reported increase in the incidence of SE over the past two decades.[13 14] The nature of the databases in those studies did not allow for a sub-analysis of trends in the incidence and mortality of generalised convulsive and non-convulsive SE respectively. Overall the reported age-standardised mortality rate for SE of approximately 0.2/100,000[12] is comparable to that seen in our study yet reasons for the failure to see a similar decrease in SE mortality over the last decade are not immediately evident. Whilst differences in SE mortality rates (which were broadly similar) may be partially explained by different coding systems, it is unlikely to be the explanation for the difference in mortality rates as the rate of misclassification of the primary cause of death would not be expected to differ significantly from year to year.[5] More plausible explanations may be

variation in population demographics, with a higher incidence (and mortality) of SE in non-white populations[15], differences in healthcare access in the US[12] and differences in attribution of cause of death (e.g. status epilepticus in coma may be more likely to be classed as a cause of death in one country rather than another).[16] This underlines the need for a uniformly accepted definition and classification of SE such as that recently proposed by the ILAE Task Force[4], and perhaps more pertinently in the context of mortality, one for non-convulsive SE.

One of the major limitations of this study is that it provides a snapshot on national mortality data for Epilepsy and SE without the corresponding incidence rates. Consequently we are unable to comment on whether there has been an increase in the incidence of SE since 2001 (in line with the US Studies), or whether the observed decrease in SE mortality is mirrored (and therefore partially explained) by a corresponding decrease in the incidence of SE. This merits further study. Indeed the primary alternative hypothesis for the observed fall in SE mortality is that this is due to a corresponding fall in the incidence of SE due to possibly improved treatments. This is nevertheless counterintuitive, as it would not be expected that there would be such a difference between the UK and the US. The change in temporal definition (to an earlier time point) would, if anything, lead to a greater number of epilepsy-related deaths being classified as SE-related, which would, in turn, increase (not reduce) the number of SE deaths (and therefore cannot explain our results). A further limitation of the current study is that it only examines mortality trends since 2001. This, however, is in line with our hypothesis that the advocacy for more aggressive and earlier treatment of prolonged seizures, as mandated by Lowenstein and colleagues,[3] was the catalyst for improved SE management and prognosis. Changes in the national coding system (from WHO ICD-9 to ICD-10) also determined our cut-off point.

In summary our finding supports the hypothesis that the policy of early and aggressive treatment of SE may be improving the prognosis of this condition in England and Wales. Our figures are similar to those obtained for SE associated deaths in the US[11,12], where a similar

trend for fewer SE deaths was however not found. There may be a number of explanations for this difference including differences in the structures of and access to health care systems and methodological considerations in the attribution of cause of death.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1: Epilepsy and Status Epilepticus Mortality (Crude and Age-Adjusted) rates in England & Wales 2001-13.

Year	Population	Total epilepsy deaths	Crude epilepsy mortality (per 100,000)	Age-adjusted epilepsy mortality (per 100,000) (95% CI)	SE deaths (total %)	Crude SE mortality (per 100,000)	Age-adjusted SE mortality (per 100,000) (95% CI)
2001	52,359,978	1,014	1.94	3.53 (3.31–3.74)	87 (8.6)	0.17	0.32 (0.25–0.39)
2002	52,602,143	953	1.81	3.07 (2.87–3.26)	91 (9.5)	0.17	0.32 (0.25–0.38)
2003	52,863,238	1,075	2.03	3.56 (3.35–3.78)	85 (7.9)	0.16	0.28 (0.22–0.34)
2004	53,152,022	980	1.84	3.28 (3.07–3.48)	85 (8.7)	0.16	0.29 (0.23–0.35)
2005	53,575,343	1,059	1.98	3.5 (3.29–3.71)	77 (7.3)	0.14	0.25 (0.19–0.31)
2006	53,950,854	1,018	1.89	3.32 (3.12–3.53)	84 (8.3)	0.16	0.28 (0.22–0.34)
2007	54,387,392	998	1.83	3.19 (2.99–3.39)	69 (6.9)	0.13	0.22 (0.17–0.27)
2008	54,841,720	1,045	1.91	3.33 (3.13–3.53)	66 (6.3)	0.12	0.21 (0.16–0.26)
2009	55,235,253	1,016	1.84	3.16 (2.97–3.35)	79 (7.8)	0.14	0.25 (0.19–0.30)
2010	55,692,423	1,006	1.81	3.07 (2.88–3.26)	55 (5.5)	0.10	0.17 (0.13–0.22)
2011	56,170,927	1,006	1.79	3.07 (2.88–3.26)	69 (6.9)	0.12	0.19 (0.15–0.24)
2012	56,567,796	1,066	1.88	3.02 (2.83–3.20)	80 (7.5)	0.14	0.20 (0.15–0.24)
2013	56,948,229	1,040	1.83	3.02 (2.84–3.20)	68 (6.5)	0.12	0.18 (0.14–023)

Figure 1: Trends in age-adjusted non-SE Epilepsy (red) and SE (black) mortality rates with 95% Confidence Intervals (dotted lines) in England & Wales 2001-2013.