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Statistical Process Control (SPC)—A simple objective method for monitoring seizure frequency and evaluating effectiveness of drug interventions in refractory childhood epilepsy

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Summary
Introduction: Objective assessment of seizure fluctuation in patients with refractory epilepsy in the clinical setting is difficult and subjective assessment may lead to inappropriate changes in medication. We therefore evaluated the utility of Statistical Process Control (SPC) charts as a simple objective clinical tool to demonstrate variability in seizure frequency and to assess the efficacy of drug interventions.
Methods: Total weekly seizure frequencies over 1 year were collected for 38 young people with refractory epilepsy. SPC I-charts were generated and Nelson's tests for ''special'' causes of variability applied. In a separate analysis, run charts were reviewed by two epileptologists blinded to clinical data who were asked to identify if and when drug interventions took place.
Results: The SPC charts showed that only seven out of 38 (18%) patients had stable seizure frequencies. In the others, they identified significant but short-lived increases in seizure frequency, which were followed by rapid return towards baseline independently of drug changes. A substantial reduction in seizure frequency was associated with a drug increase in only 5 (6.5%) instances. Inter-rater agreement on whether there were drug interventions and their timing was poor ($\kappa = 0.15$, $p = 0.4$).

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Conclusions: SPC I-charts have the potential to be used as a clinical tool to monitor seizure frequency and to evaluate efficacy of drug interventions in patients with refractory epilepsy. Epilepsy is commonly an unstable condition with fluctuations in seizure frequencies which are unpredictable and usually do not require a change in treatment. Positive responses to treatment changes are uncommon.

Introduction

Epilepsy is the most common treatable serious neurological disorder in childhood. Although most epilepsies respond to a single or a combination of antiepileptic drugs (AEDs), between 20 and 30% of patients fail to achieve seizure freedom despite appropriate therapy (refractory to treatment) (Sander, 1993). The management of such patients is often challenging as the fluctuation of seizure frequency observed in these patients makes judgements on whether a change in seizure frequency requires a change in therapy extremely difficult (Shorvon, 1996; Raspall-Chaure et al., 2008).

In most chronic conditions (e.g. epilepsy, diabetes mellitus, hypertension) there is natural variability in severity over time independent of therapeutic intervention. An appreciation of this usual variability is important when assessing the usefulness of a drug intervention; otherwise, natural changes in disease severity (e.g. seizure frequency in patients with epilepsy) may be incorrectly attributed to either worsening of the disease or to changes in therapy. Therefore, there is a need for a simple to use, effective, objective tool to help patients, their families, and medical professionals to understand natural fluctuations in seizure frequency and to evaluate effectiveness of an intervention in individuals with refractory epilepsy. We hypothesise that Statistical Process Control (SPC), which has already been applied in health care evaluation and in clinical settings such as monitoring the care of patients with asthma and diabetes mellitus, offers considerable potential as such a tool (Thor et al., 2007). We recognise that no statistical tool can replace clinical judgement, but if effective, such a tool can act as a useful adjunct in making clinical decisions.

SPC evolved in the manufacturing industry and revolutionised the understanding of variability in the measured output of industrial processes. It allowed individual measurements to be categorised as being the result of ''common'' causes of variation, which in the industrial setting, should not be followed by adjustments to the manufacturing process as the system was ''stable''. When ''special'' causes of variation are identified investigation is essential and this may lead to changes and improvements in the manufacturing process (Shewhart, 1986). Prior to the development and use of SPC, inappropriate changes were being made to ''stable'' manufacturing processes with ''common'' cause variation. This resulted in increase rather than a decrease in the variability of the manufactured products. This increased variation around specification proved a major problem when mass-production began with individual components being produced separately and then brought together for assembly. Nelson's eight tests for ''special'' causes were a later refinement, which further increased the sensitivity of SPC in identifying variations away from stable processes within systems (Nelson, 1984).

SPC charts are commonly generated using statistical packages such as SPSS or Minitab, which are expensive and may not be easily available especially in resource poor countries. Another option is to use the statistical computing environment R which is freely available but has a steep learning curve and is not widely known outside academia (R Development Core Team, 2008). Since we wanted a simple to use, inexpensive but efficient tool that can be readily accessed and used by clinicians, the patients and their carers, we developed a unique program that generates SPC charts in Microsoft Excel in a short 3 step process and can be downloaded free from our website www.ncype.org.uk/epilepsy/seizurechart.

In the current study, we aimed to study a group of children with refractory epilepsy to;

1. Investigate the potential of SPC as a simple clinical tool to improve understanding of variability in their seizure frequency and to better assess the effects of drug interventions.
2. Evaluate whether drug interventions resulted in an objective change in seizure frequency (''special'' cause variation).

Patients and methods

The National Centre for Young People with Epilepsy (NCYPE) is the United Kingdom's leading provider of education, treatment and residential care for children and young people with severe epilepsy. Located in Surrey just outside Lingfield, it has on-site 24-h medical services. All young people have very close supervision by carers throughout the days and nights. Seizure diaries are used in similar organisations such as NCYPE and have been used in previous studies to monitor seizure frequency and severity (Haut et al., 2007). Students at NCYPE have seizure diaries kept by carers who are all trained in the recognition and documentation of seizures. Entries are recorded on a daily basis and the results of the diaries play a major role in carers and medical staff assessing whether there have been substantial changes in seizure frequency and or severity. Thus, much detail and attention is given to their completion and accuracy. The work was registered as a retrospective case-note audit at NCYPE and, as such, did not require review or approval by any Research Ethics Committees in the UK.

Forty children and young adults with epilepsy were randomly selected and clinical data including age, sex, seizure types and frequency, neuroimaging findings, EEGs, AEDs at the start of the study and at the end of the study were extracted from the clinical notes using a standardised proforma. Complete data were available for 38 patients and these were included in the current study. Total weekly seizure frequencies over a period of 1 year (starting in September 2004) were collected retrospectively for all the participants. Antiepileptic drug loads for individual patients were calculated as Prescribed Daily Dose (i.e. the dose a patient takes of that drug per day), divided by the Defined Daily Dose i.e. the average maintenance dose of the drug for its main indication (PDD/DDD) (Deckers