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General review

Rates of serum level determinations of antiepileptic drugs in accord with guidelines: A clinical study at a tertiary center

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ABSTRACT

Objective. – To compare our rates of appropriate therapeutic drug monitoring (TDM) with those defined in the French guidelines for measuring drug levels of antiepileptic drugs (AEDs) during the pre- and post-medical/pharmaceutical interventional periods.
Methods. – This study was prospectively carried out at a tertiary center (epilepsy unit of the Pitié-Salpêtrière Hospital in Paris) between 2013 and 2016 over three time periods. Criteria for appropriateness were those stated in the current French guidelines. The main outcome measure was the percentage of drug level measurements with an appropriate indication, while a second outcome measure was the impact of education on clinical practice.
Results. – Of the 698 AED level measurements requested, 84% overall were found to have appropriate indications ranging from 75% to 90%, according to French guideline criteria. Rates of appropriate indications for the three most commonly used individual AEDs—valproate, carbamazepine and lamotrigine—were 79.6%, 77.3% and 90.7%, respectively, whereas the requests considered to not have an appropriate indication involved the majority (63.5%) of cases of routine drug monitoring. In addition, dedicated education seems to substantially increase rates of appropriateness.
Conclusion. – At our center, 84% of AED level determinations had an appropriate indication according to a priori defined and reliable criteria. Moreover, it was noted that a specific educational intervention substantially increased rates of appropriateness. Thus, it appears to be crucial to ensure that medical and paramedical staff are aware of the official recommendations to avoid taking unnecessary drug level measurements.

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1. Introduction

Epilepsy is one of the most common disorders for which therapeutic drug monitoring (TDM) has been used for optimizing pharmacotherapy. The concept of TDM rests on the assumption that drug concentrations correlate better with clinical effects than do dosages. Despite the considerable interpatient variability in the concentration of antiepileptic drug (AED) that produces an optimal therapeutic response, and the lack of randomized studies demonstrating a positive impact of TDM on clinical outcomes in epilepsy patients [1], TDM continues to play a role in epilepsy management; indeed, guidelines concerning their appropriateness have been proposed by the International League Against Epilepsy (ILAE) [2]. According to the ILAE, situations in which AED measurements are most likely to be of benefit include:

- establishing the therapeutic concentration at which a patient has attained the desired clinical outcome;
- helping to diagnose clinical toxicity;
- helping to assess compliance, particularly in patients with uncontrolled or breakthrough seizures;
- guiding dose adjustments in cases associated with increased pharmacokinetic variability (such as in children, the elderly, patients with other concomitant diseases, drug-formulation changes);
- anticipating potentially important pharmacokinetic changes or drug interactions (such as in pregnancy, or when an interacting drug is being added or removed);
- making dose adjustments for AEDs with dose-dependent pharmacokinetics, particularly phenytoin.

At the same time, the French National Health Authority (HAS) [3] has also provided some simplified guidelines on the appropriateness of TDM in epileptic patients, and identified five situations in which monitoring AEDs is recommended:

- suspicion of non-compliance;
- exacerbation or resurgence of epileptic seizures;
- clinical signs of overdose;
- suspected pharmacokinetic interactions or non-linear pharmacokinetic profiles;
- specific conditions are involved (such as pregnancy, status epilepticus, metabolic failure).

In an ideal environment, drug levels would only be requested for an appropriate indication [4], as per these guidelines. Indeed, it is obvious that monitoring serum levels of AEDs in selected patients and in special situations is likely to be more rewarding and less expensive than routinely taking such measurements in every patient attending a large clinic [5]. However, in a large hospital with a high staff turnover, the appropriateness of serum level determinations of AEDs in accordance with the guidelines may be less relevant. In any case, continuing education among members of the team on the criteria for rational drug level requests is certainly required [6].

The present study was performed to assess the percentage of serum level determinations for AEDs that fulfilled the current criteria for appropriate drug level monitoring in hospitalized patients at different time points (before and after education on TDM appropriateness). The main outcome measure was the percentage of measurements with an appropriate indication. The second outcome measure was the impact of education on clinical practice.

2. Material and methods

2.1. Setting

The present study was prospectively carried out at the epilepsy unit of the Pitié-Salpêtrière Hospital in Paris between 2013 and 2016 during three periods (period 1, period 2 and period 3) of several months each. Participants included non-consecutive adult epileptic patients of both genders and any age group taking the usual therapeutic dose of AEDs, and undergoing drug monitoring during their hospitalization.

Specific education on the criteria defining rational drug level requests was delivered to the medical staff between periods 1 and 2.

2.2. Appropriateness criteria

A dedicated questionnaire was filled in for each patient by both the pharmacy and medical residents. A detailed history of their epileptic fits, specific AED prescribed and reason for medical hospitalization was systematically detailed.

The following criteria had to be fulfilled to assess whether an AED level determination request was appropriate: suspicion of non-compliance; clinical signs of overdose; exacerbation of epileptic seizures; suspicion of pharmacokinetic interactions; and non-linear pharmacokinetic profile.

Excluded from the study were patients with specific conditions (such as pregnancy, status epilepticus, metabolic failure) for whom AED level determinations are always systematically assessed at our epilepsy unit.

2.3. Measurement of AED levels

AED measurements were taken using the immunochemical method, and all were systematically performed at the Pitié-Salpêtrière Hospital except for measurements of oxcarbazepine, clobazam and clonazepam, all of which were outsourced.

2.4. Intervention

The resident pharmacist retrospectively and systematically assessed whether the indications for a TDM request were appropriate; if not, then some suggestions were given. Also, a standard indication checklist for TDM based on HAS guidelines was provided for all new medical residents.

2.5. Statistical analysis

Data were presented as medians with the corresponding range or as percentages with 95% confidence intervals (95% CIs) calculated according to standard procedures. The effect of

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