Therapeutic drug monitoring in epilepsy treatment

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Findings by SBU Alert

Drug monitoring as a means to adapt the dosage of antiepileptic drugs to achieve a particular concentration in blood is well documented. However, there are few studies showing the extent to which drug monitoring contributes toward greater effectiveness in epilepsy treatment as measured by better seizure control. The findings of SBU Alert show that there is currently poor* evidence to demonstrate the benefits of the method for patients.

Hence, it is essential to assess patient benefits and costs, and how to optimally use the method.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see “Grading of evidence”.

Alert is a joint effort by the Swedish Council on Technology Assessment in Health Care (SBU), the Medical Products Agency, the National Board of Health and Welfare, and the Federation of Swedish County Councils.

Technology

Therapeutic drug monitoring (TDM) involves the management of drug doses based on drug concentrations measured in blood plasma or serum. Blood samples are collected from patients and analyzed at designated laboratories. Hence, the dose can be adjusted to achieve a concentration within a targeted therapeutic range where the greatest effects can be expected at the lowest risk for side effects.

Different patients require different doses of a drug to achieve a particular effect and to avoid side effects. The main reason for this is that different individuals metabolize drugs at different rates, and hence concentrations in blood vary widely. By knowing which concentration yields the best effects, doses can be adjusted to each patient.

Therapeutic drug monitoring is used in many different types of treatment. Important areas today include, eg, treatment using psychotropic drugs for depression and schizophrenia, treatment of certain heart diseases, and certain types of asthma treatment. The method has received greatest attention in situations where it is difficult to manage therapy based only on the clinical effect, particularly when the goal is to prevent symptoms and where failure of treatment may have severe consequences. For these reasons, therapeutic drug monitoring has become important in treating epilepsy, where therapy aims at reducing the risk for new seizures. This method is by no means new. It was introduced toward the end of the 1960s and has been used routinely since the 1970s for treating epilepsy. The method has received renewed attention due to the recent debate concerning overuse and incorrect application of therapeutic drug monitoring [1]. Studies from Sweden also show substantial variation in practice in different parts of the country.

Target group

An estimated 60 000 individuals in Sweden have active epilepsy, approximately 4400 new cases appear each year. Most patients with active epilepsy are treated by drugs and are therefore potential candidates for therapeutic drug monitoring.

Relation to other technology

The alternative to therapeutic drug monitoring is to adjust the dose solely according to the clinical effects achieved. This means that the prescribing physician increases the dose when effects are poor, ie, seizure, and reduces the dose when symptoms of overdosing appear. This presumably creates a greater risk that patients will be exposed to side effects or unnecessary seizures due to insufficient doses, which in turn may have both medical and economic consequences.

Patient benefits

Ideally, randomized studies should be used to assess the benefits of therapeutic drug monitoring, where treatment results are compared among patient groups who either received or did not receive data on concentrations in treatment. Relevant measures of the effects can therefore be the percentage of patients who are free from seizures or experience some reduction in the number of seizures, or the time that it takes to achieve full seizure control.

Very few studies have systematically analyzed the importance of therapeutic drug monitoring on the effects of epilepsy treatment. A literature search identified only one prospective randomized study [2]. In this study, 127 epilepsy patients were randomized either to treatment with or treatment without the support of therapeutic drug monitoring. Samples were taken from patients in both groups, but only in one group were the attending physicians given the results. 105 patients complied with the planned 1-year followup. No differences were found in seizure control. However, a large percentage of the patients, equally large in both groups, showed drug levels outside of the target area. A possible conclusion here is that the attending physicians did not use the drug monitoring information, which may have contributed to the negative result. Such a conclusion would concur with the results of a retrospective analysis of 164 patients [3]. Patients' seizure control during 1 year prior to the introduction of TDM was compared with the situation after this service became available. The patients' seizure control had improved only in cases where the attending physician used the information from the analysis in a goal-oriented way.

The sparse documentation may be somewhat explained by the fact that the method was established early, but also by methodological problems. Namely, there is a range of circumstances which can affect and complicate the interpretation of certain analytical values, but also complicate the assessment of benefits in TDM of various antiepileptic drugs. Factors which should be taken into consideration when assessing this method include:

- Characteristics of the referring physician/purchaser.

This may concern the competence of the referring physicians and the issues which they address in their analysis. Practical issues of importance include the extent to which the referral for TDM contains the information required for accurate interpretation of the results and if the sample is drawn at the right time.

- Type of analysis and reliability of the method.
- Level of service concerning the analysis.

If the analysis is performed and the results are returned on site in connection with a patient visit, or at a central laboratory where the results may take several days. Are the results given only as a numerical value of drug concentration, or does the service include a clinical pharmacological assessment and advice concerning dose changes?

- The drugs which are targets for analysis.
- Characteristics of the patient population, eg, severity of illness.

Given the wide variations in conditions, it is difficult from individual studies to draw general conclusions concerning the value of drug analysis for epilepsy treatment. Research in the field has focused on sub-issues such as how different antiepileptics are metabolized in the body and the relationship between a given dose and the serum concentration achieved. Large individual differences have hence been shown. Other areas that have been addressed include which drug concentrations yield the best effects in most patients [4,5] and the extent to which access to TDM is responsible for patients being treated at drug levels within the recommended target areas. Open, nonrandomized studies have shown that after the introduction of a TDM service most patients are treated using drug concentrations within the target ranges [6,7], and that the method is used in a more goal-oriented way if it is related to a comprehensive pharmacokinetic service [8,9].

Complications and side effects

The complication risks in relation to taking samples for drug analysis are negligible. Over-interpretation or inaccurate interpretation of TDM results may, of course, involve certain risks due to unmotivated dosage adjustments. This has been discussed, but the risk has not been quantified.

Costs and cost-effectiveness

The costs for various drug analyses depend on what is included in the method/service, and this varies. Certain laboratories provide results only in the form of the measured values placed in relation to a so-called target range. Others include a more or less qualified clinical pharmacological assessment of the results, with an individual, written response. The response is based on the results of the analysis and information and questions in the referral. The costs also vary depending on the type of drug and the analytical method.

According to a survey conducted in 1990, approximately 100 000 analyses of antiepileptic drugs are conducted annually in Sweden [10]. This corresponds to nearly two analyses per treated patient and year. Given an estimated average price of 150 SEK per analysis and 50 SEK for collecting the sample, the annual costs would be approximately 20 million SEK. This can be viewed in relation to other costs for epilepsy care, eg, the total costs for sales for antiepileptic drugs in Sweden during 1997 of approximately 120 million SEK. It may also be of interest to compare the costs for inpatient care services related to epilepsy. During 1994 in Sweden, 47 517 patient days (9317 admissions, average length of stay 1.5 days) were attributed to epilepsy and 12 887 (5 603) admissions, average length of stay 2.3 days) to convulsions. At an average cost per patient day of 2700 SEK, the annual cost for inpatient care services

due to epilepsy and convulsions is approximately 160 million SEK. Hypothetically, if the use of therapeutic drug monitoring would reduce the average length of stay for epilepsy by one day, this would result in a savings of approximately 25 million SEK. However, data of this type is lacking as is knowledge about the methods cost effectiveness expressed in, eg, SEK per seizure-free day.

Diffusion in Sweden

Analysis of antiepileptic drugs is offered by a large number of clinical chemical and pharmacological laboratories (both under private and county council ownership) throughout Sweden. This method is available and used everywhere in Sweden. However, there are indications that utilization varies by health service region.

An international quality control program was established in the 1970s. It is reasonable to require laboratories that offer this type of analysis to be associated with such a program.

Current evaluation research

Projects related to analysis of antiepileptic drugs are being conducted at many sites in Sweden and internationally. These studies mainly address issues concerning drug metabolism, individual differences in this regard, genetic background to individual variations, and the association between concentrations and effect. Other projects address new technologies for collecting samples. An Italian multicenter study is the only known ongoing randomized study to evaluate the effects of therapeutic drug monitoring on the treatment results for epilepsy.

Expert

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