

Therapeutic drug monitoring of valproic acid through plasma concentration

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Introduction

Therapeutic drug monitoring is the measurement of specific drug and/or their breakdown products (metabolites) at timed intervals to maintain a relatively constant concentration of the medication in the blood. Some of the monitored drugs tend to have a narrow "therapeutic index", which is a ratio between the toxic and therapeutic (effective) dose of medication.

Burtn et al. (2006) have shown that valproic acid is an 8-carbon 2-chain fatty acid that is metabolized by the liver and processed at a variable rate based on the patient's liver function and age, in addition to patient's other routine medications with which valproic acid may interact. At therapeutic concentrations, valproic acid mediates prolonged recovery of voltage-activated Na⁺ channels, thereby inhibiting repetitive firing induced by depolarization of cortical and spinal cord neurons.

Unborn babies exposed to valproate are at very high risk of neurodevelopment disability and other birth defects and the need for effective contraception planning must also be emphasized, along with the requirement for specialist oversight to safely change their medication if planning a pregnancy according to Marshall and Bangert (2008).

The determination of an antiepileptic drug concentration is recommended as a baseline

measurement after starting drug therapy, according to NICE Clinical Guideline 137 (2020), after a change in the drug dose regimen, after addition of a second drug that may interact with the antiepileptic drug, and after a change in the patient's liver, cardiac, or gastrointestinal function. According to NICE Clinical Guideline 38 (2020), measurement of an antiepileptic drug concentration is usually performed after 4 to 5 elimination half-lives of drug administration, that is, once a steady state concentration has been achieved.

Materials and methods

This is a retrospective study on 40 patients over the period from January the 9th to March the 11th 2020. All serum samples were selected from specimens submitted to the laboratory for routine antiepileptic drug testing for valproic acid. The analyses were performed using an automated analyzer Immulite 2000, competitive immunoassay methods for the quantitative measurement of valproic acid. The Immulite 2000 is an automated random access analyzer that uses chemiluminescence technology.

The therapeutic range for valproic acid is 50-100 mcg/mL, sub-normal level is < 50mcg/mL, and the toxic level is > 100 mcg/mL.

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Result and discussion

In this study were analyzed 40 patients coming from the department of neurology and psychiatry, patients with epilepsy or with bipolar mood disorders and other neuralgia. Males represented 37.5% of the total number of patients, and females 62.5%, which is 25% more than males, showing that females are more vulnerable. Standard deviation for patient's age within this population with 95% confidence interval was 45.9 ± 5.4 years. Female only, has shown lower age standard deviation with 95% confidence interval of 32.5 ± 2.5 years. Approximately 42.5% of the population were with normal serum level of valproic acid (50-100 mcg/mL), and 57.5% were with sub-normal serum level of valproic acid (< 50 mcg/mL), and none with toxic level of valproic acid (> 100 mcg/mL) in serum samples. Within 95% confidence interval, serum levels were measured to be 46.4 ± 7.5 ($\pm 16\%$) mcg/mL. Mean of inter-individual variability in valproic acid serum concentrations were 38.9% CV for dose of 400mg/day, 45.8% CV for dose of 600 mg/day, and 14.25% CV for dose of 800 mg/day.

As demonstrated (Warner et al., 1998), many of the drugs that require therapeutic monitoring are taken for a lifetime. They must be maintained at steady concentrations year after year while the person ages and goes through life events that may alter that individual's therapeutic level, including pregnancies, temporary illnesses, infections, emotional and physical stresses, accidents, and surgeries.

Tests that measure drug concentration in serum are used to monitor blood levels of drugs that have a narrow range in which the drug is effective, but not toxic. It was shown that no toxicity was found and therapeutic response was satisfying within 42.5% of the patients. There is significant number of patients (57.5%) with sub-normal serum level of valproic acid, partially because this low level has satisfactory therapeutic response, but there is still chance for non-compliance. In addition, Shaikh (2018) demonstrated that some drugs require monitoring because the dosage of drug given does not correlate well with the concentration of drug that may reach the blood. Sometimes, the way that a drug is absorbed and metabolized can vary from person to person, or the physical or health status of a person

can affect the drug level in the blood. Through years of testing, the optimum therapeutic ranges for drugs have been determined. In these ranges, most people will be effectively treated without excessive side effects or symptoms of toxicity.

Conclusion

Patients treated with valproic acid are most likely woman at the age of 30-35 years, still in reproductive period and have childbearing potential. This fact requires protection for girls and young women, and using valproic acid only when other medications have not been tolerated or have been found to be ineffective. It is vital where valproate is prescribed to girls and women of childbearing potential that they are made aware of the risks of taking the medication in pregnancy. Sub-normal level of valproic acid in serum is partially because this low level has satisfactory therapeutic response but there is still chance for non-compliance.

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