ABSTRACT

Title

Estimation of total and free phenytoin concentration in low albumin patients admitted in critical care

Background

Phenytoin has been widely used in the prophylaxis and treatment of epilepsy. However, dosing phenytoin is challenging because it exhibits non linear pharmacokinetics, zero order elimination and a multitude of drug interactions. Phenytoin is also highly protein bound (90%). It is the unbound or free form which can cross the blood brain barrier and causes both the therapeutic and toxic effects. A fall in serum albumin concentration can alter phenytoin binding capacity. In this situation, estimating total phenytoin concentration which includes the bound and unbound portions will provide discrepant results compared to the actual free phenytoin concentration.

Aim

- To compare free phenytoin concentration measured by three methods (Direct serum measurement, Routine method and by the Sheiner Tozer calculation method).
- To estimate total phenytoin concentration by two method (Direct serum measurement and Sheiner Tozer calculated total method) and if feasible, to

develop a model to predict the free measured phenytoin concentration from total phenytoin concentration.

Methods:

This was an observational study. Patients in the Medical Intensive Care Unit who were on phenytoin, were observed from the day of admission. When serum albumin level was <3.5 g/dL, blood samples were collected prior to phenytoin administration in patients. Direct measurement of total and free phenytoin concentration was done by High Performance Liquid Chromatography. Free phenytoin was also estimated by the Sheiner Tozer equation and routine method (Direct measured total/10).

Results:

The total and free phenytoin concentration was measured in 57 patients with low albumin. The median and interquartile range for direct measured total and Sheiner Tozer calculated total phenytoin concentration was 9.82(6.02-13.85) and 17.14(10.63-24.53) respectively. There was a mean relative difference of 42% in the total phenytoin direct measured concentration compared to the Sheiner Tozer calculated total phenytoin. Seventy five % of patients if reported only using the direct measured concentration would have total phenytoin concentration within the therapeutic range, whereas these patients would be supratherapeutic by the

Sheiner Tozer calculation. These patients would require a reduction in the phenytoin dose, which would be unlikely if the clinician's judgement is based ONLY on the direct measured total phenytoin.

The median (IQR) for routine, direct measured and Sheiner Tozer free phenytoin was 0.98 (0.60 - 1.39), 1.92 (1.06 -2.76) and 1.71 (1.06 - 2.45) respectively. The correlation coefficient (r^2) for direct measured with routine free phenytoin and with Sheiner Tozer calculated free concentrations was found to be 0.63 and 0.64 respectively. And if the phenytoin concentration was reported using the Sheiner Tozer calculated total, 33% of patients would be falsely reported as therapeutic whilst being supratherapeutic in the direct measured free method.

Conclusion:

Our study concluded that the total phenytoin concentration based on the Sheiner Tozer corrected equation is different from the direct measured concentration by High Performance Liquid Chromatography, in patients with low albumin. In addition, free phenytoin concentration can only be reported from a direct measured value and not any prediction/equation.

Keywords

Total phenytoin concentration, free phenytoin concentration, low albumin, Critical care, Sheiner Tozer Equation, High Performance Liquid Chromatography