Free phenytoin assessment in patients: measured versus calculated blood serum levels

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Abstract

Background: Total serum drug levels are routinely determined for the therapeutic drug monitoring of selected, difficult-to-dose drugs. For some of these drugs, however, knowledge of the free fraction is necessary to adapt correct dosing. Phenytoin, with its non-linear pharmacokinetics, > 90% albumin binding, and a slow elimination rate, is such a drug requiring individualization in patients, especially if rapid intravenous loading and subsequent dose adaptation is needed. In a prior long-term investigation, we showed the excellent performance of pharmacy-assisted Bayesian forecasting support for optimal dosing in hospitalized patients treated with phenytoin. In a subgroup analysis, we evaluated the suitability of the Sheiner-Tozer algorithm to calculate the free phenytoin fraction in hypoalbuminemic patients.

Objective: To test the usefulness of the Sheiner-Tozer algorithm for the correct estimation of the free phenytoin concentrations in hospitalized patients.

Setting : A Swiss tertiary care hospital.

Method : Free phenytoin plasma concentration was calculated from total phenytoin concentration in hypoalbuminemic patients and compared with the measured free phenytoin. The patients were separated into a low (35 ≤ albumin ≥ 25 g/L) and a very low group (albumin < 25 g/L) for comparing and statistically analyzing the calculated and the measured free phenytoin concentration.

Results : The calculated (1.2 mg/L (SD = 0.7) and the measured (1.1 mg/L (SD = 0.5) free phenytoin concentration correlated. The mean difference in the low and the very low albumin group was: 0.10 mg/L (SD = 1.4) (n = 11) and 0.13 mg/L (SD = 0.24) (n = 12), respectively. Although the variability of the data could be a bias, no statistically significant difference between the groups was found: t test (p = 0.78), the Passing-Bablok regression, the Spearman's rank correlation coefficient of r = 0.907 and p = 0.00. The Bland-Altman plot including the regression analysis revealed no systematic differences between the calculated and the measured value [M = 0.11 (SD = 0.28)].

Conclusion: In absence of a free phenytoin plasma concentration measurement also in hypoalbuminemic patients, the Sheiner-Tozer algorithm represents a useful tool to assist therapeutic monitoring to calculate or control free phenytoin by using total phenytoin and the albumin concentration.

Published in : Int J Clin Pharm.2016;38(2):303-9 doi: 10.1007/s11096-015-0241-x.
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