EDITORIAL

Drug Levels in ICU – T or F

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The recommended dose of a drug is usually determined on the basis of studies performed on healthy volunteers.[1] However, drug pharmacokinetics in the critically ill are very different from those in healthy volunteers.[2] The volume of distribution may increase due to increased cardiac output, aggressive fluid therapy, and leaky capillaries. Organ dysfunction may affect the metabolism and clearance of the drug. Other drugs which have been prescribed might interact with the drug and affect its levels. In critically ill patients, the net result of these conflicting influences on the level of a drug is difficult to predict. The recommended dose of a drug might, therefore, reach levels that are either so low as to be ineffective or so high as to be toxic.

Monitoring of drug levels is therefore recommended in order to ensure both efficacy and safety of drugs.[3] Regrettably, it is the total drug level that is often measured. For drugs that are highly protein-bound, estimation of total levels can lead to erroneous conclusions. Albumin levels often decrease in critically ill patients. In these instances, the measured total drug levels may be low when in fact the free levels of the drug (which are the effective levels) are high. This might lead to an erroneous increase in the dose of the drug which might raise levels of the free drug to toxic levels.

Phenytoin is the prototypical example of a drug-affected by this misinterpretation of total levels.[4] Doses of phenytoin are usually adjusted on the basis of total phenytoin levels. Merely dividing the total levels by 10 to get an estimate of the free levels is nearly the same as the measurement of the total levels. The Sheiner–Tozer equation attempts to predict free levels more accurately because it incorporates the albumin levels in its formula.[5]

In this issue of the journal, Wilfred et al.[6] have demonstrated that in critically patients with low albumin levels, even the Sheiner–Tozer equation may not be completely accurate. Though the equation is quite precise in predicting subtherapeutic levels of phenytoin, in patients with therapeutic and supratherapeutic levels (estimated by direct measurement of free levels), the equation performs inconsistently. Estimation of total phenytoin levels or merely dividing total levels by 10 is the most inaccurate. This method clearly underestimates free phenytoin levels and, more worryingly, fails to identify supratherapeutic levels in nearly 90% of patients.

Adjustment of phenytoin doses on the basis of free phenytoin levels is therefore desirable. It might not always be possible to measure free phenytoin levels, however. Using the Sheiner–Tozer equation is a suboptimal but the next best option. Making therapeutic decisions on the basis of total phenytoin levels (or directly derived free levels) must be avoided in critically ill patients.

Phenytoin is often being replaced by levetiracetam in many ICUs. Unlike phenytoin, levetiracetam is not protein-bound (10%) and is not vulnerable to the problems faced by phenytoin.

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Nevertheless, this study by Wilfred et al. conveys a very important lesson. Whenever the levels of a highly protein-bound substance are being measured in the ICU, whether it is an antibiotic, an antifungal agent, an anti-seizure agent, an immunosuppressant, or a hormone, ideally, free levels of the substance should be measured. If it is not possible to measure the free levels, the clinician should be aware of the fallacies of total drug level measurements while making therapeutic decisions.

Personality traits can be divided into thinkers (T) vs feelers (F).[7] T types tend to be more scientific and more objective, whereas F types tend to be more emotional and subjective. While there will always be a debate about the relative merits of each personality type, there is no argument that measurement of free levels of protein-bound molecules, F is clearly superior to T.

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