Understanding tools

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In this issue of the Journal, Schumacher and colleagues report on a case of methylene blue–induced serotonin syndrome after left ventricular assist device implantation. The complication of serotonin syndrome has been described in a number of cases after cardiac surgery, as summarized in the article. Because serotonin syndrome is a clinical entity rarely encountered by cardiac surgeons, the perspective of the nonsurgeon author group is appreciated. Some additional background on this syndrome and its diagnosis, however, should be considered. In the realm of cardiothoracic surgery, we have become accustomed to increasingly sophisticated and precise diagnostic tools: conventional angiography is supplemented by objective measurements such as fractional flow reserve or intravascular ultrasonography; the diagnosis of aortic stenosis is refined by a number of hemodynamic measures; and predicted perioperative risk is quantified by risk calculators. How does the evaluation of serotonin syndrome in the setting of cardiac surgery compare?

Schumacher and colleagues assert that the Hunter criteria have 97% specificity for the diagnosis of serotonin syndrome. A review of the article by Dunkley and coworkers describing the development of this tool gives some context. First, serotonin toxicity is defined as a triad of (1) autonomic signs, (2) neuromuscular changes, and (3) altered mental status, with the corollary that “[o]mitting any of these parts in the assessment of the patient may lead to an inaccurate diagnosis of serotonin toxicity and false assumptions about the most useful diagnostic symptoms.” This creates a potential dilemma for evaluation in the postoperative setting, in which autonomic signs and mental status may be confounded by such factors as systemic inflammatory response, cardiopulmonary status, and effects of anesthetic or opioid medications. Dunkley and coworkers recognized that “serotonin toxicity is currently too incompletely defined to be a prognostically useful clinical diagnosis,” that there was no criterion standard for the clinical diagnosis, and that the entity “is not a discrete syndrome, but rather a spectrum of toxicity.” With regard to the Hunter criteria, the method of criteria development was described as “arbitrary.” The Hunter criteria were derived solely from a data set of patients suffering from selective serotonin reuptake inhibitor overdoses. Patients with life-threatening serotonin toxicity or other confounding medications were excluded. This limitation casts doubt on the validity of this tool for populations that are not well represented by the initial sample. Further questions are raised by the statistical methods. After an initial univariate analysis, logistic regression analysis was not used because of the combination of a limited data set and large number of predictor variables. Rather, the classification and regression tree analysis was used. Although we do not claim to be familiar with the intricacies of this technique, known limitations include the inability to consider relationships among input variables, a sensitivity to outliers, an inflexibility to missing data, the potential for overfitting, and high variance across samples. In the neurologic literature, the validity and superiority of the Hunter criteria have lately been challenged.

There are thus a number of issues with the tool itself and its application to postoperative cardiac surgical patients that may render invalid the quoted 97% specificity. Although Schumacher and colleagues describe a rather comprehensive workup to exclude other diagnoses, the fact remains that this is a rather fuzzy diagnosis, especially when attempting to draw conclusions from an assembly of case reports. Accordingly, we counsel the readers of the Journal to appreciate the case report as an interesting read and caution against looking much deeper.
References


