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Letter to the Editor

Response to the Letter to the Editor: Arrhythmias in the pediatric intensive care unit: a prospective study of the rates and predictors of arrhythmias in children without underlying cardiac disease

Keywords: Aminophylline; arrhythmia; pediatric intensive care unit; cardiac

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Dear Dr Axelrod and editors of *Cardiology in the Young*, we greatly appreciate the commentary by Axelrod et al[1] on the risk of arrhythmias with aminophylline use in the postoperative cardiac care of children. Their recent, well-designed, prospective investigations have not revealed an increased risk of cardiac arrhythmias in children undergoing repair for CHD.[2] These publications have added significant data on the risk of arrhythmias with aminophylline use in critically ill children after the publication of our prospective evaluation published in 2015.[3]

In their single-centre, randomised clinical trial, Axelrod et al included 144 patients after cardiac surgery involving cardiopulmonary bypass. Although the authors concluded that aminophylline postoperatively did not attenuate acute kidney injury, administration was determined to be safe with similar rates of adverse events between placebo and treatment groups. Their investigation demonstrated no increased risk of cardiac arrhythmias in patients without a previous arrhythmia history.[2] In our investigation, we intentionally excluded patients with cardiac disease because the risk of arrhythmias in postoperative cardiac patients is seemingly greater than other paediatric ICU patients for numerous reasons. These reasons for increased arrhythmia risk, as also discussed in the commentary, include myocardial incisions during surgery, fluid and electrolyte shifts after cardiopulmonary bypass, haemodynamic abnormalities leading to atrial stretch or poor myocardial perfusion, anatomical and electrophysiological substrates in patients with previous repair for CHD, and use of exogenous catecholamines and inotropic medications.[1] Although conventional wisdom would suggest that the use of aminophylline would further increase the arrhythmia burden in this vulnerable population, their study provides further evidence as to why well-designed, randomised trials are so important in challenging conventional wisdom.

As noted in their letter, one important distinction between our study and that of Axelrod et al was the co-administration of albuterol to our patients. The patients who experienced arrhythmias in our study while receiving aminophylline infusions were also on albuterol and had low therapeutic aminophylline drug levels of 9.1 and 7.5 mcg/ml. On univariable analysis, albuterol use was not a statistically significant factor associated with arrhythmia development. A limitation of our analysis, however, was that the arrhythmia event rate was quite low, and the low event rate limited our ability to add numerous additional variables to the multivariable model. It is possible that it is the combination of intravenous aminophylline with an inhaled β2-agonist that provides the greatest risk for developing tachyarrhythmias.

Although there are limited data suggesting an increased arrhythmia risk with aminophylline use in asthmatics, there are also little data suggesting that aminophylline should be used for critically ill patients with asthma. A Cochrane review in 2012 by Nair et al[4] concluded that intravenous aminophylline in conjunction with standard β2-agonist therapy did not result in significant bronchodilation, but carried an increased risk of arrhythmia development. In that review, 25 of 100 patients treated with aminophylline experienced arrhythmias or palpitations, compared with 10 of 100 in the control group. Dalabih et al[5] also concluded that, after adjusting for asthma severity, the addition of aminophylline to corticosteroids and inhaled β-agonists was associated with

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statistically and clinically significant increases in paediatric critical care unit length of stay and time to symptom improvement. The National Asthma Education and Prevention Program published their most recent guidelines for management of acute asthma exacerbation, and methylxanthines such as aminophylline were not recommended.[6] In the emergency department, aminophylline appears to provide no additional benefit to optimal short-acting beta agonists and increases the frequency of adverse effects.[7] Even as failing to show a reduction in nebulised treatments or length of hospital stay in children, studies have actually shown increased toxicity in those being treated with methylxanthine for severe asthma exacerbation.[8] Therefore, although the data from Axelrod et al would suggest that there is no additional arrhythmia risk in postoperative cardiac patients, the combination of a possible arrhythmia risk in the asthmatic population, coupled with limited clinical benefit, would leave the authors to question the use of aminophylline in patients with asthma exacerbations.

In summary, the commentary and more recent data from Axelrod et al provide insight into arrhythmia risk with use of intravenous aminophylline, and their data suggest that the risk of arrhythmias may be lower than that previously believed. As their data have demonstrated no increased arrhythmia risk in postoperative cardiac patients, a cohort of patients that should be at a greater risk of arrhythmias, the authors applaud the call for further investigations of the arrhythmogenic effects of aminophylline and look forward to additional published data.

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