ORIGINAL ARTICLE

Optimal Dose of Adenosine Effective for Supraventricular Tachycardia in Children

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ABSTRACT

Objective: To determine the optimal adenosine dose effective in supraventricular tachycardia (SVT) and underlying conditions affecting the effective dose in children.

Study Design: Experimental study.

Place and Duration of Study: Department of Cardiology, The Children's Hospital and Institute of Child Health, Lahore, from July 2008 to June 2011.

Methodology: All children presenting with SVT were administered adenosine in rapid boluses according to PALS guidelines using incremental doses of 100, 200 and 300 µg/kg. The response was recorded on 12 lead ECG. Pre-excitation was documented and echocardiography performed on all children after attaining sinus rhythm. Mann Whitney test and Kruskal-Wallis test were used as a test of significance to determine any difference in effective adenosine dose between normal heart and various underlying conditions, taking $p < 0.05$ as significant.

Results: Eighty five patients were treated for 110 episodes of SVT with adenosine. M:F ratio was 2.2:1. Their age ranged from 6 days to 14 years with mean age of 27.9 months. Adenosine was effective in reverting 97 episodes of SVT to sinus rhythm (88.2%). A dose of upto 100 µg/kg was only effective in 36.4% episodes of SVT. Two hundred µg/kg was effective in 44.3% of those not responding to 100 µg/kg dose (n = 31/70, cumulative 64.5%). A dose of 300 µg/kg was effective in further 25 patients not responding to lower doses (n = 25/38, 65.8%; cumulative 88.2%). Mean effective dose of adenosine was 185.3 $\pm$ 81.0 µg/kg with median effective dose of 200 µg/kg. Significantly higher dose of adenosine was required in children with underlying pre-excitation, n = 18/97 (220.8 $\pm$ 67.6 µg/kg vs. 177.2 $\pm$ 81.9 µg/kg, p = 0.039).

Conclusion: Adenosine is an effective medicine in treating SVT in children. A higher dose of 200 µg/kg may be used as first bolus particularly in children with pre-excitation.

Key words: *Adenosine. Supraventricular tachycardia. Children. Dose.*

INTRODUCTION

Supraventricular tachycardia (SVT) is the most common tachyarrhythmias in children. Atrioventricular reciprocating tachycardia (AVRT) is much more common than atrioventricular nodal re-entrant tachycardia (AVNRT).[1] The cardiac output is rate dependant in children with much limited cardiac reserve. As a result, these tachyarrhythmias are poorly tolerated and potentially fatal in children when compared to adult population.[2] Adenosine is a purine nucleotide proven very effective in controlling these tachyarrhythmias.[3] Since, the initial clinical trials in late 1980s, the adequate dosage of adenosine has been questioned. Initial trials used doses in range from 35 to 75 µg/kg.[4,5] Later studies supported evidence of higher doses of adenosine for optimum results in children. AHA and PALS recommend starting bolus of 100 µg/kg followed by increments of 100 µg/kg to a maximum of 300 µg/kg.[6] The dose of adenosine, although well defined in adults, is not adequately established in children.

In this study, the aim was to determine the optimal dose of adenosine effective in reverting SVT to sinus rhythm in children using PALS guidelines.

METHODOLOGY

The study was conducted at the Children's Hospital and Institute of Child Health, Lahore, Pakistan from July 2008 to June 2011. All patients aged from new born to 14 years presenting with SVT, diagnosed and documented on 12 lead ECG were enrolled in the study after taking an informed consent from the parents. The episodes of SVT was differentiated into AVRT and AVNRT on the basis of modified criteria taking into account the heart rate, QRS morphology, Pseudo S or Q waves in lead II, III and AVF and ST elevation or depression after 80 msec of J-point.[7-9] Patients having underlying heart blocks, bundle branch blocks, or taking any medications known to affect adenosine metabolism were excluded from the study. An algorithm was formulated for uniform management of patients with SVT according to Department's treatment protocol. Approval was sought from hospital ethics committee prior to patient enrollment. Weight was recorded in all children.

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Antecubital venous access was attained in all children using a wide bore cannula.[10] Adenosine was administered in rapid boluses according to PALS guidelines using incremental doses of 100, 200 and 300 µg/kg.

The responses were recorded on cardiac monitor and 12 lead surface ECG, where possible. The response was labelled as transient if the sinus rhythm appeared for even a single beat. The response was labelled as sustained when sinus rhythm persisted for more than 3 minutes.[11] Sinus rhythm was documented on ECG and noted for evidence of pre-excitation in form of short PR interval (< 0.08 msec) and delta wave. Echocardiography was performed on all children after attaining sinus rhythm to document any underlying congenital structural defect or dilated cardiomyopathy.

The results were tabulated and analyzed using Statistical Package for Social Science (SPSS) version 17, (Inc. Chicago, IL). The data were analyzed to determine frequencies for categorical variables including demographic profile, gender, age group (neonate, infant, child), response to adenosine at doses 100, 200 and 300 µg, evidence of underlying pre-excitation, congenital heart and recurrence. Mean, standard deviation and median were calculated for quantitative variables including age in months and responsive dose of adenosine. Frequencies and percentages were calculated for the qualitative variables including gender, age group, underlying cardiac structural and conduction defect. The effective doses and age variables did not follow normal distribution pattern. Mann Whitney test and Kruskal - Wallis test were used as tests of significance to determine any significant difference between various factors and effective adenosine dose, taking $p < 0.05$ as significant.

RESULTS

Ninety-four patients were initially enrolled in the study. Five patients were haemodynamically unstable and were cardioverted to sinus rhythm on presentation. Four patients were given verapamil as per treatment protocol due to slow SVT. Eighty-five patients were treated for 110 episodes of SVT with adenosine. The patients included 76 males (69.1%) and 34 females (30.9%) with M:F ratio of 2.2:1. The patients' age ranged from 6 days to 14 years, mean age being 27.9 months. Mean age at presentation was 23 $\pm$ 8.5 days in neonates, 4.7 $\pm$ 3.3 months (median 3 months) in infants and 88.2 $\pm$ 53.2 months (median 93 months) in children. Thirty-one episodes of SVT occurred in neonates (28.2%), 47 in infants (42.7%) and 32 children (29.1%).

Adenosine was effective in reverting to sinus rhythm in 97 episodes (88.2%) while 13 patients had to be treated with second line antiarrhythmics. A dose of 100 µg/kg was only effective in 40 episodes of SVT (36.4%), 200 µg/kg was effective in 44.3% of those not responding to the 100 µg/kg dose (n = 31/70, 64.5%). A dose of 300 µg/kg was effective in further 24 patients not responding to lower doses (n = 25/38, 65.8%).

In adenosine responsive patients, mean effective dose was 185.3 $\pm$ 81.0 µg/kg with median effective dose of 200 µg/kg (range 75 – 300 µg/kg). Mean effective dose of adenosine in neonatal age group was 196.3 $\pm$ 85.4 µg/kg (median 200 µg/kg), 193.3 $\pm$ 81.6 µg/kg (median 200 µg/kg) in infants and 163.8 $\pm$ 74.3 µg/kg (median 100 µg/kg) in children. There was no significant difference in mean effective adenosine dose in various age groups (p = 0.21).

Pre-excitation was detected in 18/97 episodes on attaining sinus rhythm (18.6%). A statistically significant higher dose of adenosine was required in children with underlying pre-excitation to revert to sinus rhythm (220.8 $\pm$ 67.6 µg/kg, median 200 µg/kg vs. 177.2 $\pm$ 81.9 µg/kg, median 200 µg/kg, p = 0.039).

In 82/97 episodes (84.5%) of SVT, there was no underlying structural defect, 4 (4.2%) had dilated cardiomyopathy and 11 (11.3%) had underlying congenital structural cardiac defect, mostly having severe pulmonary hypertension. The effective dose was lower in patients with underlying dilated cardiomyopathy (n = 4) than normal heart (n = 82), (125 $\pm$ 50 µg/kg, median 100 µg/kg vs. 184.5 $\pm$ 80.8 µg/kg, median 200 µg/kg, p = 0.19). There was no significant difference in mean effective dose of adenosine between patient with normal heart (n = 82) or congenital heart disease (n = 11), (184.5 $\pm$ 80.8 µg/kg, median 200 µg/kg vs. 213.6 $\pm$ 83.9 µg/kg, median 200 µg/kg, p = 0.26). Out of 97 responsive episodes of SVT, 57 (58.8%) were first episode, 22 (22.7%) were second episodes while 18 (18.6%) were subsequent episodes of SVT. There was no significant difference in effective dose of adenosine between first episodes (n = 57) and recurrences (n = 40, p = 0.23).

DISCUSSION

Adenosine is a purine derivative mainly affecting the AV node with very short half life. This pharmacological effect make it a very useful agent in treating SVT.[2,3] Adenosine was effective in reverting to sinus rhythm in 96 episodes (87.3%). The agent has its documented efficacy as the present results were in accordance with previous studies reporting 87 – 100% response at various incremental doses.[12-14]

A dose of 100 µg/kg was only effective in 40 episodes of SVT (36.4%). Doses upto 50 µg/kg have previously shown to have extremely poor efficacy, 6-16%.[13-15] Losek *et al*. documented a low efficacy of 22% with upto 100 µg/kg dose of adenosine.[16] In this study, though this dose showed slightly better efficacy (36.4%), it proved far less than optimal for reverting episodes of SVT to

sinus rhythm. Response to doses upto 200 µg/kg was 64.5%. This result was comparable to earlier reports having efficacy of 52.8%.[13,14]

Mean effective dose of adenosine was slightly higher than previously documented studies with mean dose of 156.5 µg/kg.[13] This difference was probably due to inconsistency of standard increments of drug boluses in the previous reports ranging from 50 to 300 µg/kg. There was no significant difference in mean effective adenosine dose in various age groups with median effective dose of 200 µg/kg. Same effective dose has been documented previously in various studies ranging from 150-200 µg/kg adenosine.[14,15] Mean effective dose was lower in patients with dilated cardiomyopathy but the difference did not reach significant levels. This subgroup of patients has not been studied independently for response to adenosine with episodes of SVT. Larger case control studies might be needed to find the optimum dose response of this specific group of patients. There was no significant difference in mean effective dose of adenosine between patients with normal heart or congenital heart disease as documented in previous studies.[7]

In this study, there was no significant difference in effective dose between neonates, infants or children. It was in contrast to previous studies where Dixon *et al*. showed higher adenosine doses required for neonates.[14] The children were not distributed in previous study on the basis of pre-excitation. A higher number of patients with AVRT may have resulted in requirement of higher doses of adenosine. Despite the difference in previous studies, median effective dose was above 100 µg/kg (i.e. 150 µg/kg and 200 µg/kg). A significantly higher dose of adenosine was required in children with underlying pre-excitation to revert to sinus rhythm. AVRT is much common in paediatric age group. On surface ECG, pre-excitation is manifested in upto 70% patients with AVRT.[17] This statistically significant difference might be only in children with manifest pre-excitation i.e. Wolff-Parkinson-White (WPW) syndrome. Patients with concealed accessory pathways did not have any significant difference in effective dose. Losek *et al*. also showed better efficacy in AVNRT than AVRT.[16] Most data from previous studies showed no difference in outcome using adenosine in both AVNRT and AVRT.[18] The effective dose in children with WPW syndrome has not been demonstrated previously. However, the refractory nature of the accessory pathway is well documented and catheter ablation is more frequently opted in the long run.[19]

Out of 97 responsive episodes of SVT, 57 (58.8%) were first episode, 22 (22.7%) were second episodes while 18 (18.6%) were subsequent episodes of SVT. There was no significant difference in effective dose of adenosine between first episodes and recurrences. The same response even at recurrences indicate fixed nature of underlying mechanism. None of the patients developed any sustained tachyarrhythmia or accentuation of AV nodal pathway despite frequent use of relatively higher doses of adenosine. It was in contrast to previous reports of occasional life-threatening tachyarrhythmias generated or accentuated by adenosine.[20,21] Mild cough was observed in 17/110 patients (15.5%) while flushing occurred in 4/110 patients (3.64%). One patient (0.9%) had significant sinus bradycardia which reverted spontaneously within 10 seconds. No sustained side effect was noted during administration of adenosine in any patient that may have required further pharma-cological intervention. These findings were also similar to reported side effects in previous studies.[20] Chest tightness, a common side effect demonstrated previously, could not be ascertained due to young age. However, cough might be a representation of same feeling in paediatric age group, which was quite frequent.

CONCLUSION

Adenosine is an effective medicine in treating SVT in children. Higher starting dose may be required in majority of children specially in those with pre-excitation. Starting dose of 200 µg/kg may be used as first bolus followed by 300 µg/kg for optimum response in children with SVT.

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