Adenosine-Induced Flow Arrest to Facilitate Intracranial Aneurysm Clip Ligation: Dose-Response Data and Safety Profile

John F. Bebawy, MD, Dhanesh K. Gupta, MD, Bernard R. Bendok, MD, Laura B. Hemmer, MD, Carine Zeeni, MD, Michael J. Avram, PhD, H. Hunt Batjer, MD, and Antoun Koht, MD

BACKGROUND: Adenosine-induced transient flow arrest has been used to facilitate clip ligation of intracranial aneurysms. However, the starting dose that is most likely to produce an adequate duration of profound hypotension remains unclear. We reviewed our experience to determine the dose-response relationship and apparent perioperative safety profile of adenosine in intracranial aneurysm patients.

METHODS: This case series describes 24 aneurysm clip ligation procedures performed under an anesthetic consisting of remifentanil, low-dose volatile anesthetic, and propofol in which adenosine was used. The report focuses on the doses administered; duration of systolic blood pressure <60 mm Hg (SBP <60 mm Hg) and any cardiovascular, neurologic, or pulmonary complications observed in the perioperative period.

RESULTS: A median dose of 0.34 mg/kg ideal body weight (range: 0.29–0.44 mg/kg) resulted in a SBP <60 mm Hg for a median of 57 seconds (range: 26–105 seconds). There was a linear relationship between the log-transformed dose of adenosine and the duration of a SBP <60 mm Hg ($R^2 = 0.38$). Two patients developed transient, hemodynamically stable atrial fibrillation, 2 had postoperative troponin levels >0.03 ng/mL without any evidence of cardiac dysfunction, and 3 had postoperative neurologic changes.

CONCLUSIONS: For intracranial aneurysms in which temporary occlusion is impractical or difficult, adenosine is capable of providing brief periods of profound systemic hypotension with low perioperative morbidity. On the basis of these data, a dose of 0.3 to 0.4 mg/kg ideal body weight may be the recommended starting dose to achieve approximately 45 seconds of profound systemic hypotension during a remifentanil/low-dose volatile anesthetic with propofol induced burst suppression. (Anesth Analg 2010;110:1406–11)

Despite advances in endovascular techniques to treat intracranial aneurysms, craniotomy for clip ligation of intracranial aneurysms remains a mainstay of definitive therapy to prevent morbidity and mortality because of growth, rupture, or rerupture of the aneurysm.1 For many aneurysms, proximal temporary arterial occlusion is used to decrease the turgor of the aneurysm neck, thereby facilitating clip ligation of the aneurysm or clip reconstruction of the native artery. It is often difficult to find an anatomically suitable place for temporary arterial occlusion for aneurysms of the intracranial carotid artery proximal to its bifurcation into the middle and anterior cerebral arteries.2-3 These aneurysms have required temporary extracranial cross-clamp of the carotid artery in the neck to facilitate intracranial clip ligation. There are alternative techniques, such as endovascular balloon occlusion with suction decompression or deep hypothermic circulatory arrest, but they require significant logistical support.4,5 In addition, these procedures may be associated with significant patient morbidity; endovascular procedures may result in dissection of friable arteries or distal arterial embolic occlusion, whereas cardiopulmonary bypass may result in arterial injury at the site of cannulation or arterial embolic phenomena related to aortic plaque. Furthermore, coagulopathies induced by cardiopulmonary bypass, independent of the required anticoagulation, result in a high incidence of postoperative intracranial hematomas.6 When temporary arterial occlusion is impractical or difficult for anatomical reasons, adenosine administration can produce brief, profound systemic hypotension and flow arrest as an alternative to logistically complex methods of decreasing parent artery blood flow.7-12

Adenosine is an endogenous purine nucleoside that slows electrical conduction through the atrioventricular (AV) node and has a negative chronotropic effect on the sinoatrial (SA) node. These pharmacologic effects produce a dose-dependent decrease in atrial and ventricular electrical activity that results in bradycardia, AV nodal blockade, and sinus pauses. In addition, the rapid decrease in heart rate results in a rapid and profound decrease in cardiac...
output and mean arterial blood pressure (MAP). When administered as an IV bolus, adenosine can produce transient asystole with concomitant flow arrest. Cardiovascular effects are transient because of the rapid plasma and tissue metabolism of adenosine. When coordinated with the activity of the neurosurgeon, adenosine-induced flow arrest can provide a “hands-free” method of facilitating aneurysm clip ligation.

Although the magnitude and duration of systemic hypotension produced by IV adenosine is dose dependent, there are limited data available to assist in the selection of an appropriate initial dose. Hashimoto et al.\(^{13}\) reported dose-response data for patients undergoing glue embolization of arteriovenous malformations. For these patients, they targeted the durations of asystole, MAP <30 mm Hg (profound hypotension), and MAP <50 mm Hg (moderate hypotension). They recommended that individual dose-response relationships in patients be established by a series of injections of escalating doses, each separated by 3 to 10 minutes. Collecting individual dose-response data, however, requires additional time and exposes the patient to profound cardiovascular perturbations that are not without potential cardiac or cerebral morbidity.\(^{10,11,14,15}\)

An estimate of the adenosine dose that would provide adequate controlled hypotension for patients undergoing intracranial aneurysm surgery would be clinically useful. In addition, this dose could be used in those cases in which the need for flow arrest was unanticipated (e.g., aneurysmal rupture). Therefore, we reviewed our clinical experience with adenosine-induced flow arrest during intracranial aneurysm surgery to estimate the dose-response relationship of patients undergoing aneurysm clip ligation under an anesthetic consisting of remifentanil, a volatile anesthetic, and propofol. Furthermore, we report the cardiovascular, pulmonar, and neurologic events that occurred in the intraoperative and immediate postoperative periods to shed light on the safety of adenosine-induced flow arrest at these points in time.

**METHODS**

We reviewed the perioperative records of all patients who consented to be in our IRB-approved intracranial aneurysm surgery database and identified those patients who received adenosine to facilitate clip ligation of an intracranial aneurysm at Northwestern Memorial Hospital between August 1, 2006, and June 30, 2009. In our clinical practice, we do not administer adenosine to patients with evidence of severe (≥80%) left main coronary artery stenosis, severe multivessel coronary artery disease (3 vessels or grafts with >80% stenosis), AV conduction defects (second degree AV block), or pacemakers. In addition, patients with severe reactive airway disease (i.e., requiring hospitalization in the previous 6 months and active perioperative wheezing) do not receive adenosine. For the patients who received adenosine after April 1, 2008, “high-fidelity” dose-response hemodynamic data were recorded by a dedicated observer (i.e., the durations of the predefined hemodynamic responses were measured and recorded). This allowed a dose-response relationship to be determined for the duration of a systolic blood pressure <60 mm Hg (SBP<60 mm Hg) and for the duration of a SBP < SBP immediately before adenosine administration (SBP<baseline).

The cardiac safety of adenosine in the immediate intraoperative and postoperative periods was evaluated by observing the occurrence of postadenosine arrhythmias. Continuous monitoring of leads II and modified V5 were used in the operating room (Datex AS/5 monitor, GE Healthcare, Waukesha, WI), while a 12-lead electrocardiogram was obtained on arrival to the postanesthesia care unit. Surveillance postoperative troponin I levels were measured on arrival to the postanesthesia care unit in 17 of 24 (71%) patients. When increased, serial troponin I levels were measured until levels began to decrease. In addition, in patients in whom troponin I levels were increased (2 of 24, 8%), transthoracic echocardiographic evaluation was performed to exclude impaired myocardial contractility or regional wall motion abnormalities. The pulmonary side effects of adenosine were evaluated by observing the peak airway pressure after drug administration intraoperatively (detected by anesthesiologist and/or ventilator high-pressure alarm if >40 cm H\(_2\)O). The incidence of new, immediate postoperative neurologic deficits in patients receiving adenosine was determined by neurosurgical house staff examinations and compared with that of a cohort of all the 162 patients who underwent craniotomy for clip ligation of an intracranial aneurysm between August 2006 and June 2008 at our institution.

All hemodynamic data are reported as median (minimum, maximum). All normally distributed demographic data (e.g., age, weight, and height) are reported as mean ± SD, and differences between the adenosine patients and the nonadenosine cohort were isolated using an unpaired t test, with a 2-tailed P < 0.05 considered significant. All categorical demographic data (e.g., sex, ASA physical status, and Hunt and Hess grade) are reported as count (frequency), and differences between the 2 groups of patients were isolated using the \( \chi^2 \) test, with a P < 0.05 considered significant. The relationship between the log-transformed dose of adenosine (normalized to the ideal body weight [IBW] in kilograms, Dose\(_{\text{IBW}}\)) and the speed of onset and duration of actions of adenosine were examined using linear regression, as preliminary analysis of the untransformed data revealed a nonlinear dose-response relationship. IBW was chosen over actual body weight because the initial volume of distribution of adenosine (i.e., the blood volume between the IV injection site and the right atrium and right ventricle) is unlikely to change with obesity.\(^{16,17}\)

To examine the possibility of a carryover effect, the dose-response relationships were determined for the initial doses of adenosine and for all the doses of adenosine. Fisher exact test was used to determine whether the use of adenosine was associated with an increased incidence of postoperative neurologic deficits, with a 2-tailed P < 0.05 considered significant. All statistical analysis was performed using SigmaStat version 3.5 (Systat Software, Chicago, IL).

**RESULTS**

Forty-two doses of adenosine were administered to 24 patients. Fourteen patients received 2 (\( n = 10 \)) or 3 (\( n = 4 \)) doses of adenosine for repositioning of the initial clip or for
placement of additional clips. These additional adenosine doses were administered after recovery of the arterial blood pressure to baseline values, approximately 2 to 10 minutes after the previous dose of adenosine had been administered, at the request of the neurosurgeon. There was no apparent tachyphylaxis to adenosine in any of these patients. Although 1 patient did not achieve asystole with any of the adenosine doses given (0.3, 0.4, and 0.5 mg/kg IBW), this patient did have a SBP of 60 mm Hg for 30 to 40 seconds after each dose, thereby allowing successful placement of multiple clips for artery reconstruction. The clinical characteristics of the 24 patients are reported in Table 1. At the time of aneurysm clip ligation, all patients were receiving an anesthetic that consisted of a potent inhaled anesthetic (0.5 minimum alveolar concentration [end-tidal anesthetic concentration at which 50% of patients do not move in response to surgical incision] of desflurane or sevoflurane), remifentanil (0.1 μg·kg⁻¹·min⁻¹), and propofol (50–150 μg·kg⁻¹·min⁻¹). No patient was receiving any antihypertensive drugs, and all patients received propofol to induce electroencephalographic burst suppression (burst suppression ratio of 0.7–0.8) at the time of aneurysm clipping.

Thirteen patients had “high-fidelity” dose-response hemodynamic data recorded from 20 doses of adenosine (Table 2). The linear regression analyses of the initial doses revealed that there was a relationship between the log-transformed normalized (to IBW) adenosine dose and the duration of SBP <60 mm Hg from the first dose administered to 13 patients in this series (raw data). Note that the x-axis is a log₁₀ scale. One patient had an aneurismal subarachnoid hemorrhage (open triangle). The solid lines depict the log-linear dose-response curves, and the dashed lines depict the 95% confidence intervals of the models. The dose-response model for these data is expressed as DurationSBP <60 mm Hg = 254.9 + 177.5 × log doseIBW (R² = 0.38).

Of the 24 patients who received adenosine, 2 developed transient and hemodynamically stable atrial fibrillation on recovery from adenosine intraoperatively. Both these patients had unruptured aneurysms (i.e., Hunt and Hess grade 0). One of these patients converted to sinus rhythm spontaneously intraoperatively, and the other required intraoperative treatment with amiodarone for conversion to sinus rhythm. Two other patients developed mild postoperative increases in troponin levels (>0.03 ng/mL), and neither of these patients demonstrated any clinical (e.g., chest pain) or transthoracic echocardiographic evidence of cardiac dysfunction (e.g., decreased contractility and regional wall motion abnormality) in the postanesthesia care unit. One of these 2 patients had a perioperative aneurysmal subarachnoid hemorrhage (Hunt and Hess grade 2). No patient had any apparent pulmonary side effects perioperatively (e.g., increase in peak airway pressure >5 cm H₂O after the administration of adenosine intraoperatively). Three of the 24 patients who...
received adenosine had a documented new postoperative neurologic deficit within 24 hours of surgery (12.5%), which was not different from the proportion in the cohort of aneurysm patients who did not receive adenosine (n = 29 of 138 patients, 21.0%, P = 0.529).

**DISCUSSION**

In this review of our clinical experience with adenosine-induced flow arrest to facilitate clip ligation of intracranial aneurysms, we observed that the coordinated administration of adenosine at a dose of 0.3 to 0.4 mg/kg IBW to patients receiving a remifentanil/low-dose volatile anesthetic with propofol induced burst suppression provided adequate transient global flow arrest and profound systemic hypotension to allow successful aneurysm clip ligation in all patients. The safety profile of our doses of adenosine, in the intraoperative and immediate postoperative periods, seemed to be acceptable; assessing long-term safety and outcomes related to these adenosine doses requires a larger prospective study. Few patients had postadenosine arrhythmias (2 of 24) or postoperative troponin I increases (2 of 24), and no patient had a perioperative pulmonary event. In addition, there was no significant difference in the proportion of patients with new immediate postoperative neurologic injuries after adenosine (3 of 24) compared with that proportion in a cohort of patients who did not receive adenosine (29 of 138). Therefore, when individual dose-response data cannot be obtained (e.g., emergent intraoperative aneurysmal rupture), or possibly should not be obtained (e.g., to avoid repeated cardiac/cerebral ischemic episodes), the coordinated administration of an initial dose of adenosine in the range of 0.3 to 0.4 mg/kg IBW should be considered to achieve approximately 45 seconds of controlled systemic hypotension when using the aforementioned anesthetic technique.

This is the largest case series of adenosine-induced flow arrest that provides dose-response guidance. Only 1 other report has described the adenosine dose-response relationship. In a series of 5 patients undergoing glue embolization, Hashimoto et al. reported a dose-response relationship based on the repeated administration of escalating test doses of adenosine to achieve 20 to 30 seconds of profound hypotension (which they defined as a MAP of 25–30 mm Hg) with the concomitant administration of sodium nitroprusside. Their dose-response models predict that a dose of 0.45 mg/kg would produce 7 seconds of asystole, 7 seconds of profound hypotension, and only 16 seconds of moderate hypotension. In fact, their models predict that a dose of 0.88 mg/kg would be required for 45 seconds of moderate hypotension and that a dose of 2.15 mg/kg would be required for 45 seconds of profound hypotension. Based on the clinical experience of one of the authors (DKG), who had extensive experience in the use of adenosine to provide flow arrest, we chose a starting dose of 0.3 mg/kg IBW for our aneurysm patients.

The adenosine doses of this study were one-fifth to one-seventh the doses predicted from the linear regression models of Hashimoto et al. There are several possible explanations for the large difference in the dose-response relationships observed in these data sets. Patients in our series had not received any antihypertensive drugs for >3 hours. In addition, these patients were all receiving an anesthetic consisting of ≤0.5 minimum alveolar concentration of a potent volatile anesthetic, ≥0.1 μg·kg⁻¹·min⁻¹ of remifentanil, and 50 to 150 μg·kg⁻¹·min⁻¹ of propofol. In contrast, the patients in the study performed by Hashimoto et al. were anesthetized with a combination of isoflurane and propofol (doses not reported), with sodium nitroprusside to attenuate possible postadenosine rebound hypertension. Although propofol and volatile anesthetics have minimal direct and indirect effects on SA and AV node conduction, the remifentanil infused as part of our balanced anesthetics profoundly depresses SA nodal activity and conduction through the AV node. In contrast, the sodium nitroprusside infused as part of the study by Hashimoto et al. has direct effects on the SA and AV nodes and indirect effects (via the arterial baroreceptor reflex) that increase electrical conduction. Therefore, the anesthetic and physiologic state of the patients in this study may have had a profound effect on the electrophysiologic state of the heart, altering the pharmacodynamics of adenosine.

The ideal method of individualizing drug administration may be based on an individual patient’s dose-response relationship, which is determined by exposure to escalating drug doses. However, with adenosine, this may not always be a practical or safe option. Individual dose-response relationships may not be previously determined for all patients, and therefore, the dose required for an emergent, unanticipated flow arrest would not be known. Administration of escalating adenosine doses required to determine an individual’s dose-response not only takes planning but also exposes the patient to multiple periods of flow arrest that have the potential to produce cardiac and neurologic injury. In a series of 15 patients receiving intermittent boluses of adenosine for placement of endovascular thoracic aortic stent grafts, Plaschke et al. found that the electroencephalogram and the serum enolase level showed no signs of cerebral ischemia, despite achieving 18 to 58 seconds of asystole. However, patients undergoing aneurysm clip ligation may be more sensitive to neuronal injury secondary to flow arrest, especially after subarachnoid hemorrhage or in the presence of vasospasm. Finally, exposure to repeated doses of adenosine may result in either a carryover effect or tachyphylaxis. If either of these phenomena occurs, the escalating doses required to delineate an individual’s dose-response relationship may inaccurately estimate the dose required at the time that flow arrest is needed for clip placement. The lack of a relationship between the pooled doses in our series and the hemodynamic endpoints, despite a strong relationship between the initial dose administered and the duration of SBP<60 mm Hg, may be due to a carryover effect. Therefore, if individualized dose-response curves are being generated, care must be taken to provide sufficient time between each dose to minimize the possible carryover effect.

Adenosine-induced flow arrest offers a unique method to reduce cerebral perfusion pressure briefly and controllably and can facilitate the clip ligation of many aneurysms that were previously treated with deep hypothermic circulatory arrest, temporary occlusion of the extracranial carotid artery, or endovascular balloon catheter retrograde
suction deflation. Although brief periods of profound hypotension can also be produced by large boluses of sodium nitroprusside or esmolol, both of these drugs are less predictable in their dose-response relationships and are associated with rebound hypertension. For giant aneurysms, repeated periods of transient flow arrest may offer an alternative to deep hypothermic circulatory arrest, thereby avoiding the coagulopathy associated with deep hypothermia as well as the coagulopathy, hyperglycemia, and rebound hyperthermia that occur after cardiopulmonary bypass. However, the periods of flow arrest must be carefully coordinated with the neurosurgeon such that adequate working time is available for the successful placement of each clip or series of clips. Adenosine offers the final advantage of being easily applicable in a variety of situations without advanced preparation or complex logistic coordination. Therefore, when an unanticipated anatomical obstacle is encountered or an aneurysm is ruptured on dissection, adenosine can be administered to facilitate surgical control.

In this observational series, the transient flow arrest and profound hypotension induced by adenosine seemed to be associated with minimal morbidity in the short term. However, our series only had sufficient statistical power to detect a 30% difference in the proportion of patients with neurologic injury after adenosine compared with our larger aneurysm surgery cohort. Clearly, factors that may worsen neurologic outcomes, such as hyperglycemia or hyperthermia, should be avoided to prevent secondary injury. As previously stated, no perioperative pulmonary complications were observed, 2 patients (2 of 24) developed hemodynamically stable and transient atrial arrhythmias after adenosine administration, and 2 other patients (2 of 24) had biochemical evidence of myocardial injury, which may or may not have been related to adenosine. However, underreporting of organ morbidity and inconsistent surveillance of biomarkers of organ function (only 17 of 24 patients in this study) may bias the incidence of complications observed in this retrospective series. Therefore, we advocate considering the placement of external defibrillator pads on all patients who might receive adenosine, to provide external pacing capability if prolonged asystole/bradycardia were to develop, or cardioversion in the face of hemodynamically unstable atrial fibrillation. In addition, monitoring all these patients for biochemical evidence of myocardial injury (e.g., troponin I) in the postoperative period has now become our standard practice to perform appropriate subsequent evaluation for those with a positive response.

An additional limitation of this retrospective case review is that the dose-response data for individual patients were collected from observations of responses of nonrandomized doses that spanned a very limited range. Although identification of the median adenosine dose associated with a 95% probability of adequate duration of flow arrest and hypotension (i.e., 95% effective dose [ED$_{95}$]) would optimally require administration of doses of adenosine spanning several orders of magnitude in a randomized order, administration of adenosine doses that are 10 to 100 times larger than the therapeutic doses is unethical. Therefore, a modification of the Dixon up-down method might be the most ethical and efficient method of determining the ED$_{95}$ prospectively.

In conclusion, for intracranial aneurysms in which temporary occlusion is impractical or technically difficult, adenosine is a viable option to provide brief periods of flow arrest for facilitating aneurysm clip ligation with apparently low neurologic and cardiopulmonary morbidity in the perioperative period. We found that, consistent with our previous clinical experience, a dose of 0.3 to 0.4 mg/kg IVB achieves approximately 45 seconds of profound systemic hypotension in aneurysm patients receiving a balanced anesthetic consisting of a low dose of volatile anesthetic and infusions of remifentanil and propofol. Refinement of the dose-response relationship and the true long-term safety of adenosine-induced flow arrest will require a more sophisticated and larger prospective study. In addition, the contribution of the background anesthetic to the adenosine dose-response relationship needs to be further investigated to determine the generalizability of this observational series.

**AUTHOR CONTRIBUTIONS**

JFB helped to design the study, conduct the study, analyze the data, and write the manuscript. DKG helped to design the study, conduct the study, analyze the data, and write the manuscript. BRB helped to conduct the study and write the manuscript. LBH, CZ, and HHB helped to conduct the study and write the manuscript. MJA helped to analyze the data and write the manuscript. AK helped to design the study, conduct the study, and write the manuscript.

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**REFERENCES**

19. Sharpe MD, Dobkowski WB, Murkin JM, Klein G, Yee R. Propofol has no direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction in Wolf-Parkinson-White syndrome during alfentanil/midazolam anesthesia. Anesthesiology 1995;82:888–95