

Adenosine-induced Ventricular Asystole to Induce Transient Profound Systemic Hypotension in Patients Undergoing Endovascular Therapy

Dose–Response Characteristics

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Background: **Adenosine-induced asystole has been used to induce transient systemic hypotension for various vascular procedures. Dose–response characteristics of adenosine-induced ventricular asystole have not been determined.**

Methods: **During endovascular embolization of cerebral arteriovenous malformations, the authors performed a series of adenosine test injections to establish a dose–response relation in each patient. After an interval of 3–10 min, the dose was escalated by 10–20 mg for each injection to achieve an end point of 20–30 s of stable mean arterial pressure (MAP) reduction to 25–30 mmHg. All patients received constant infusion of nitroprusside ($\approx 1\ \mu g \cdot kg^{-1} \cdot min^{-1}$) throughout the procedure.**

Results: **The authors studied four adult patients (age, 22–44 yr; two patients had two separate procedures) and one pediatric patient (age, 4 yr). Twenty-three adenosine injections resulted in measurable asystole. The adenosine dose was 0.98 ± 0.40 mg/kg (mean ± SD), and the dose range was 0.24–1.76 mg/kg (6–90 mg). The duration of asystole, MAP < 30 mmHg, and MAP < 50 mmHg, were 8 ± 3 s, 18 ± 12 s, and 50 ± 29 s, respectively. The minimum MAP and the MAP for the first 20 s were 16 ± 3 mmHg and 30 ± 9 mmHg, respectively. There was a linear relation between adenosine dose and the duration of hypotension with MAP < 30 mmHg and MAP < 50 mmHg.**

Conclusions: **In the dose range studied, a series of adenosine test injections can be used to determine optimal adenosine dose for induction of transient profound hypotension. (Key words: Cerebrovascular disease; induced hypotension; interventional neuroradiology.)**

ADENOSINE, an endogenous purine nucleoside, induces transient atrioventricular blockade by suppressing sinus and atrioventricular node conduction. A lower intravenous dose (3–12 mg) is commonly used as an antiarrhythmic agent. Higher doses cause high-degree atrioventricular blockade, resulting in ventricular asystole and profound hypotension. Adenosine-induced transient asystole has been used to facilitate cerebral aneurysm clipping,[1] endovascular repair of thoracic aortic aneurysms,[2] and coronary artery bypass grafting.[3] We recently reported the first application of adenosine-induced asystole for endovascular glue embolization of cerebral arteriovenous malformations (AVMs).[4]

Although this technique is promising and potentially can be used for various vascular procedures, one practical problem is estimating the optimal adenosine dose to provide a sufficient duration of asystole or profound hypotension. There has been no quantitative assessment of bolus adenosine when used to induce transient profound hypotension to date. We reviewed a series of AVM embolizations and assessed dose–response characteristics of adenosine used to induce transient profound arterial hypotension.

Methods

After obtaining institutional approval and informed consent from patients, patients with angiographically documented extremely high-flow AVMs were selected for adenosine-induced asystole to induce transient profound systemic hypotension.

Monitoring included noninvasive blood pressure, pulse oximeter, capnometer, esophageal temperature, five-lead electrocardiogram with continuous ST-segment analysis, and arterial pressure from a femoral arterial introducer sheath. A transvenous right ventricular pacing wire (VSC-7; transvenous bipolar; Bard, Billerica, MA) through femoral vein after end parenthesis and external pacing–defibrillator pads (Zoll, Burlington, MA) were placed.

In adult cases, general anesthesia was induced with propofol, and succinylcholine was used to facilitate endotracheal intubation. In the single pediatric case (patient E), general anesthesia was induced with sevoflurane, and rocuronium was given before endotracheal intubation; anesthesia was maintained with isoflurane, propofol, nitrous oxide, and oxygen. Before adenosine injections, nitrous oxide was discontinued, and patients were ventilated with 100% oxygen.

We performed a series of adenosine test injections to

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Table 1. Demographic Information

Patient	Sex	Age (yr)	Weight (kg)	Height (cm)
A*	Male	44	85	175
B*	Female	42	66	160
C	Female	40	51	167
D	Female	22	61	173
E	Female	4	17	105

* Patient A and B underwent two separate procedures.

establish a dose–response relation in each patient. Test injections were made by bolus injections of adenosine through the central venous catheter. For the initial dose of adenosine test injection, 0.25–0.35 mg/kg was used. The dose was escalated by 10–20 mg for each injection with an interval of 3–10 min to an end point of achieving 20–30 s of stable mean arterial pressure (MAP) reduction to 25–30 mmHg. Sodium nitroprusside infusion ($\approx 1\ \mu g \cdot kg^{-1} \cdot min^{-1}$) was titrated to lower the baseline MAP by approximately 10% before adenosine test injections, and continued at the same rate throughout the procedure in an attempt to minimize postadenosine rebound hypertension.

Continuous recordings of electrocardiogram (lead II), arterial pressure, and central venous pressure were collected using the MacLab system (AD Instruments, Adelaide, Australia). We analyzed the following three descriptive durations: (1) asystole defined as the longest R-R interval observed after adenosine injection; (2) hypotension with MAP $<$ 30 mmHg; and (3) hypotension with MAP $<$ 50 mmHg. The adenosine effect on MAP was characterized in the following ways: (1) MAP for the first 20 s after the last R wave before the initiation of asystole (average of arterial pressure over 20 s); (2) minimum MAP during asystole; and (3) baseline MAP measured at 5 s before adenosine injection.

Data are presented as mean values ± SD. Pooled scattergrams including all adenosine injections for all procedures were constructed for (1) duration of asystole, (2) duration of MAP $<$ 30 mmHg, (3) duration of MAP $<$ 50 mmHg, and (4) MAP for the first 20 s. For each patient, a scattergram for adenosine dose and the duration of hypotension $<$ 30 mmHg was constructed. The pooled and individual scattergrams were examined by linear regression.

Results

There were four adult patients (age, 22–44 yr) and one pediatric patient (age, 4 yr; patient E). Demographics are shown in table 1. A total of 29 injections of adenosine were performed during seven procedures in five patients. Patients A and B each had two separate procedures on different dates. Twenty-three injections resulted in nonconducted P waves and were used for analysis.

Two to five test injections of adenosine were performed to estimate the optimal dose. The dose of adenosine predicted to be optimal by test injections provided sufficient duration of profound hypotension to perform a slow, controlled injection of n-butyl cyanoacrylate (NBCA) glue into the AVM nidus, as assessed by the attending interventional neuroradiologist (J.P.S.). There were no long-term complications. One patient developed transient atrial flutter after adenosine injection that spontaneously resolved after several minutes.

The adenosine dose was 0.98 ± 0.40 mg/kg (mean ± SD), and the dose range was 0.24–1.76 mg/kg (6–90 mg). The durations of asystole, MAP $<$ 30 mmHg, and MAP $<$ 50 mmHg were 8 ± 3 s, 18 ± 12 s, and 50 ± 29 s respectively. Minimum MAP and MAP for the first 20 s were 16 ± 3 mmHg and 30 ± 9 mmHg. Scattergrams of pooled data for duration of asystole, duration of hypotension with MAP $<$ 30 mmHg and 50 mmHg, and MAP for the first 20 s as a function of adenosine dose are shown in figures 1A–D. There appeared to be a linear relation between adenosine dose (milligrams per kilogram) and the duration of asystole ($y = 2.3x + 5.8$; $r = 0.28$), adenosine dose and the duration of MAP $<$ 30 mmHg ($y = 22.9x - 4.0$; $r = 0.75$), adenosine dose and the duration of MAP $<$ 50 mmHg ($y = 55.3x - 3.5$; $r = 0.74$), and adenosine dose and MAP for the first 20 s ($y = -18.3x + 47.0$; $r = 0.82$).

In each patient, there was a linear relation between adenosine dose and the duration of hypotension $<$ 30 mmHg ($r = 0.82$–0.99); the range of individual slopes was 3.7–44.1.

Discussion

This is the first report to provide dose–response characteristics of adenosine when used to induce asystole and transient profound hypotension. In each procedure, there was a linear relation between adenosine dose and the duration of hypotension (*i.e.*, MAP $<$ 30 mmHg and $<$ 50 mmHg) in the dose range studied (notwithstanding that one case had only two points). The duration of hypotension appeared to be predicable using a series of test injections. In this series, the duration and degree of hypotension induced by adenosine were sufficient to provide optimal conditions for endovascular embolization of AVMs without causing serious adverse effects. Our data should assist in formulating a protocol for the estimation of optimal dosing in future clinical studies of adenosine-induced transient profound hypotension.

The ideal method for achieving flow arrest in vascular surgery should have (1) predictable effects, especially degree and duration of hypotension; (2) few pharmacologic side effects; (3) titratability; (4) technical feasibility and simplicity; and (5) low risk for procedure-related

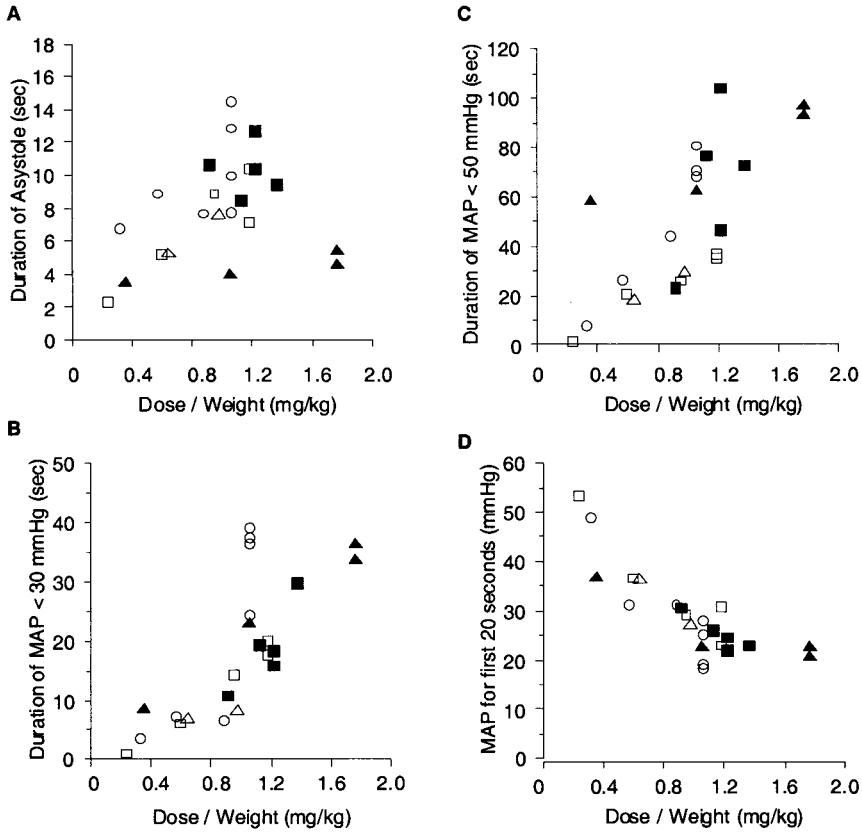

Fig. 1. Scattergrams of pooled data from five patients. Expressed as a function of dose/weight (mg/kg). Open circles = patient A; filled squares = patient B; open squares = patient C; open triangles = patient D; and filled triangles = patient E. (*A*) Duration of asystole; (*B*) duration of mean arterial pressure (MAP) < 30 mmHg; (*C*) duration of MAP < 50 mmHg; and (*D*) MAP for the first 20 s.

complications. In addition to conventional induced hypotension, there have been several methods proposed for flow arrest: balloon inflation proximal to surgical area,[5] asystole induced by adenosine,[1–4,6,7] and ventricular fibrillation induced by an alternating current through transvenous pacing electrodes.[8] Adenosine-induced blood flow reduction has several potential theoretical advantages. First, adenosine has an extremely short half-life, < 1.5 s in blood, which enables rapid, spontaneous offset. Second, side effects from bolus adenosine are not generally serious; they are transient because of rapid metabolism.[9]

When an adenosine bolus injection is used with continuous infusion of nitroprusside, the course of change in mean arterial pressure can be characterized by an immediate decrease to the minimum pressure during asystole, gradual increase during high-degree atrioventricular block, rapid return to a normal range beginning with the return of normal sinus rhythm, and modest rebound hypertension. Rapid induction of profound hypotension by adenosine bolus is advantageous when relatively precise timing is required. Abrupt increases in systemic pressure may affect stabilization of embolic materials or endovascular devices immediately after their placement. In this series, rebound hypertension was modest, partly because of our expectant use of a nitroprusside infusion aimed to lower the baseline MAP by approximately 10% before adenosine administration.

A potential problem using adenosine-induced asystole during a vascular procedure is an unexpected early return of ventricular contraction.[8] Somewhat to our surprise, early ventricular contraction did not significantly increase the MAP—profound hypotension persisted for approximately 5–15 s after return of ventricular contraction. This may be partly because of our concomitant use of nitroprusside infusion. However, nitroprusside infusion was maintained at the same rate throughout the procedure, and we would speculate that similar hemodynamic responses would result from adenosine injection without nitroprusside infusion. Because it is the induction of decreased perfusion pressure that affords "flow arrest," the duration of hypotension with MAP < 30 mmHg appears to be most clinically relevant, rather than the duration of ventricular asystole.

Other issues to be determined in future studies include the extent and relevance of transient cerebral ischemia, site of injection (central versus peripheral), and interaction with other drugs as discussed by other investigators.[2–4,6,10,11] Continuous infusion of adenosine does not appear to result in tachyphylaxis.[12] Although we did not observe tachyphylaxis in this study, the potential for its occurrence after repeated bolus administration of adenosine remains to be investigated.

In summary, we have shown dose–response characteristics for bolus adenosine used for providing transient profound hypotension that is clinically useful for various

vascular procedures. Clinically reliable individual dose–response data can be obtained by several test injections, and the duration of profound hypotension can be optimized. Our data can provide the basis for adenosine dose estimation protocols for future studies; however, the safety and effectiveness of this method remains to be determined.

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