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Case Report

A Case of High-dose Adenosine Usage for Anterior Communicating Artery Aneurysm Clip Ligation: What is the Dose Limit for a Resistant Response?

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Abstract

Intraoperative adenosine is used to induce asystole to facilitate clip ligation of intracranial aneurysms. Typically, 5–10 mg doses are used per administration and approximately 30 mg is used for a given case. An obvious concern with using adenosine is that the patient can remain in asystole or that prolonged hypotension can result in cerebral or cardiovascular ischemia. The upper limit of adenosine administration remains unclear. We present a case of a patient with a large anterior communicating artery aneurysm requiring large doses of adenosine, far exceeding previously reported cases. The patient received a 90 mg dose of adenosine to achieve 5 s of asystole as well as 30 s of hypotension that facilitated vessel dissection and clip application. Moreover, in order to successfully clip his aneurysm, he received a total of 744 mg of adenosine. After each administration of adenosine, his heart rate and blood pressure returned to baseline without the need for chest compressions or other interventions. He tolerated the procedure and had a good neurological outcome. This case is the first report of using such a high dose of adenosine in intracranial aneurysm surgery and suggests that more aggressive administration of adenosine during aneurysm clipping is feasible. Transient hypotension, as seen in this report, can provide surgeons the crucial moments they need to safely secure an aneurysm from circulation.

Keywords: *Adenosine, aneurysm, asystole, cerebral, clip, high-dose, human*

Introduction

The treatment of cerebral aneurysms has evolved over the last 15 years.[1] While many aneurysms that were previously clipped are now coiled, clip ligation remains the mainstay of treatment for large and complex aneurysms. Adenosine-induced asystole is a tool that has been useful in aiding surgeons to effectively treat these lesions, allowing them to expose the aneurysm, to identify feeding arteries, and finally to apply a clip to the neck of the aneurysm.[2,3] The amount of adenosine administered ranges from 12 to 60 mg/dose with a total drug dose between 18 and 100 mg.[3] Given the relatively recent use of adenosine in cerebral aneurysm surgery, it is unclear how much adenosine can be safely given.

We present a patient with a large, unruptured anterior communicating artery aneurysm. Intraoperative dose titration revealed that 90 mg of adenosine was required to induce 5 s of asystole. This dose was administered 7 times in order to successfully clip the aneurysm, resulting in the patient receiving a total of 744 mg of adenosine – the highest amount recorded in the literature. Postoperatively, the patient made an excellent recovery and was discharged from the hospital neurologically intact.

Case Report

A 68-year-old male was seen in the Emergency Department for evaluation of altered mental status and personality changes. His initial work up included a computerized tomography (CT) scan of his head, which was concerning for an intracranial aneurysm. There was no evidence of subarachnoid hemorrhage. A diagnostic angiogram revealed an anterior communicating artery aneurysm directed anteriorly, superiorly, and medially and measuring 17.3 mm × 15.4 mm × 15.0 mm with a 3.5 mm neck [Figure 1].

Past medical history included well-controlled hypertension, bipolar

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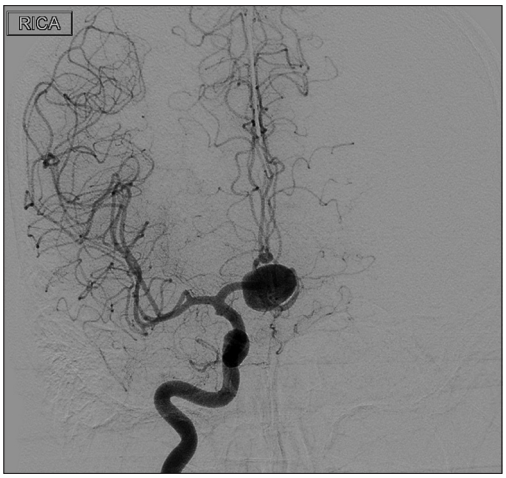

Figure 1: Diagnostic cerebral arteriogram: Anterior–posterior view

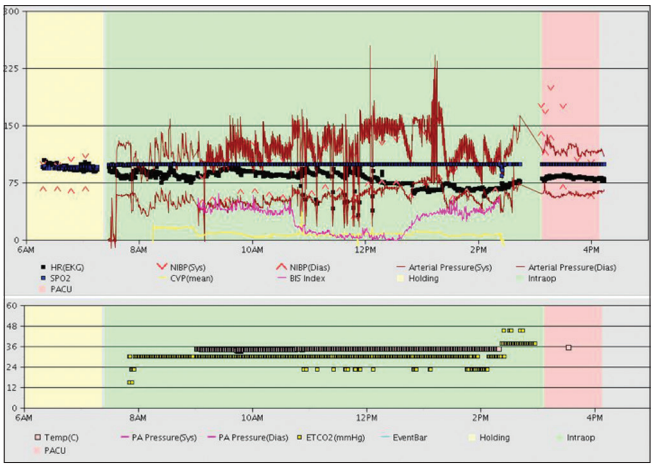

Figure 2: Anesthesia intraoperative flow sheet: The arterial pressure is represented in red. The black squares represent the heart rate

disorder and relapsing alcohol abuse. Physical examination revealed a well-appearing man in no distress. He was 178 cm and 100 kg. His blood pressure was 110/65 mmHg, heart rate 111 beats/min and regular, and his oxygen saturation was 98% on room air. He was alert and oriented to person, place, date, and situation. He had no neurological deficits.

The patient was brought to the operating room for elective clip ligation of the aneurysm. Anesthesia was induced with lidocaine, fentanyl, propofol, and succinylcholine and maintained with propofol/remifentanil infusion following endotracheal intubation. A left radial arterial catheter and a left subclavian central venous catheter were placed. Defibrillating/pacing pads were placed as a routine in our institution when intraoperative adenosine administration is anticipated. A standard right fronto-temporal craniotomy was performed to approach the aneurysm. Burst-suppression was induced with a propofol bolus of 150 mg and an increase in its infusion to 250 mcg/kg/min 5 min before the anticipated temporary clipping of the aneurysm feeding branches [Figure 2]. The decision to use adenosine was made due to the challenging size and location of the aneurysm that would allow for a transient circulatory arrest, which would aid in the dissection and treatment of the aneurysm.[2,3] The dose of adenosine was quickly escalated from 6 to 18, 30, and 60 mg due to inadequate response (our institutional goal is 30 s of cardiac asystole/severe hypotension). With the adenosine dose of 60 mg, the asystole only lasted for 2–3 s or appeared as a few skipped beats, and the systolic blood pressure decreased to about 60 mmHg and lasted for about 20 s before a quick and complete recovery. The decision to administer 90 mg of adenosine was then made. This resulted in a 5 s asystolic period and a decrease in systolic blood pressure to about 45 mmHg for approximately 30 s. No further escalation in adenosine dose was attempted even though this response was not considered optimal. After the first 90 mg of adenosine, the surgeon discovered that there was significant calcification at the aneurysm neck, and the transition zone between the calcified wall and normal endothelial surface was friable. The aneurysm ruptured during the course of clip reconstruction of the flow. During the ensuing course, 6 additional doses of 90 mg adenosine were administered. The intervals between the adjacent doses were 17, 12, 4, 7, 5, and 14 min (6 intervals for 7 doses). The responses to each succeeding adenosine (90 mg) were similar to the first dose. A full hemodynamic recovery (of the hypotension) was achieved before each re-dosing. Phenylephrine infusion continued, and intermittent boluses were given for blood pressure support. Burst-suppression based on bispectral electroencephalogram monitoring was maintained throughout [Figure 2]. Shortly following the last dose of adenosine, the surgeon was able to finish the microsurgical clip to a satisfactory result. A total of 744 mg of adenosine was administered. The patient was kept intubated overnight and extubated the next day. The patient did not have focal neurological deficits and was transferred out of intensive care unit on postoperative day 3 and discharged home 5 days later.

Discussion

We report a case of cerebral anterior communicating artery aneurysm clipping in which a total of 744 mg adenosine was administered in 11 divided doses, with the maximal dose of 90 mg being administered 7 times. To the best of our knowledge, this is the largest adenosine usage, in terms of the multitude of dosing, the maximal dose, and the total dose, ever reported for a single intracranial aneurysm microsurgical clipping. Even though we were not able to achieve a satisfactory standstill circulation condition, the severe hypotension and thus a low flow state still helped the surgeon to successfully clip-isolate this complex and complicated aneurysm. This unprecedented adenosine usage did not inflict neurological and cardiac complications in this particular patient. Postoperative electrocardiogram and troponin levels demonstrated no evidence of cardiac

injury. Similar doses have been safely used in endovascular thoracoabdominal aneurysm repair.[4]

This unique case poses two important questions: is there a dose limit for an adenosine resistant situation and what is the mechanism for the resistance? The safe usage of adenosine bolus to facilitate intracranial aneurysm clipping by creating a standstill systemic and cerebral circulation has been documented in a few cases and small single-center series reports.[2,3,5-9] In probably the largest single-center series, Bendok *et al*. summarized their experience of 40 aneurysm clippings (10 ruptured, 30 unruptured) in which adenosine was used.[5] The maximal dose in this series was 60 mg, and there were no patients who received more than 3 doses.[5]

In this case, we were essentially not able to achieve a longer than 5 s asystole even with 90 mg of adenosine bolus. It appeared that we never accomplished flow arrest even though the severe hypotension lasted for about 30 s with a 90 mg of adenosine bolus. Of note, we routinely maintained a background phenylephrine infusion, which undoubtedly counteracted some of the adenosine-induced hypotension, in order to facilitate normal systemic hemodynamics during maintenance anesthesia. Indeed, the clinical impression was that both the intraluminal pressure and flow were significantly lowered in the surgical field and that the procedure was still facilitated to a satisfactory endpoint even though no complete flow arrest was accomplished.

Adenosine is a purine nucleoside that acts through the G-protein-coupled adenosine receptor.[10] There are four subtypes of adenosine receptors, which exist in varying amounts in different tissues. The A1 receptor mediates bradycardia, through decreased atrioventricular conduction, while the A2A and A2B subtypes mediate vasodilatation/hypotension.[10] Adenosine is metabolized quickly by enzymatic breakdown, by deamination to inosine, by erythrocyte, and endothelial uptake.[11] Its plasma half-life is <10 s.[12]

While the dose–response of adenosine is generally linear,[4] inter-individual variability is not well understood. We did not pursue doses larger than 90 mg in our patient since we had achieved adequate surgical results and were concerned about safety. The etiology of the apparent adenosine resistance seen in our patient is poorly understood.

Nearly 30 years ago, it was reported that individuals in a cardiac electrophysiologic study had a 7-fold range of effective doses on a per kilogram basis.[11] One patient was taking theophylline and did not respond to doses up to 450 mcg/kg. Methylxanthines and caffeine are known to be competitive inhibitors of adenosine at the adenosine receptor.[13] However, our patient was not taking any offending agents. Second, it is also possible that genetic variations in adenosine receptor number or sensitivity, or in downstream signaling could account for inter-individual differences. Third, ABC transporters are present in various tissues and create inter-individual resistance to purine nucleoside medications.[14] However, we could not find any published data to suggest that this mechanism would affect adenosine pharmacodynamics. Finally, although we used a central line for bolus administration of the drug, an anatomic variation in venous anatomy resulting in delayed delivery to the heart and/or excessive mixing with venous blood could in theory affect drug efficacy.

Conclusion

We present a case in which large doses of intravenous adenosine failed to produce the desired duration of transient asystole. This case highlights the known variability in adenosine effects among individuals. We recommend that adenosine be titrated to individual dose–response. Further, we point out that satisfactory operative conditions may be obtained by the transient hypotension alone, without concomitant asystole.

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Conflicts of interest

There are no conflicts of interest.

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