Intravenous caffeine: An alternative to aminophylline to reverse adverse effects during regadenoson myocardial perfusion imaging

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Aminophylline has long been used in the reversal of vasodilators used for myocardial perfusion imaging. However, in 2010, manufacturers of aminophylline reported shortages making a search for an alternative a high priority. In this issue of the *Journal*, Doral et al¹ at the University of Rochester report their evaluation of the effectiveness of intravenous (IV) and oral caffeine as an alternative to IV aminophylline in the reversal of adverse effects of regadenoson. They randomized 241 patients to receive 100 mg of IV aminophylline, 60 mg of IV caffeine, or a caffeinated beverage, either diet soda or caffeinated coffee, if adverse symptoms occurred. They provided a 5-minute delay before offering a reversal agent to allow for adequate myocardial extraction of the radiotracer. Exercise was encouraged during administration of regadenoson and performed in 22% of patients.² The primary endpoint was complete resolution (CR) of symptoms. If a patient did not achieve CR, they were classified into incomplete response (IR), predominant response (PRE), partial response (PR), or no response (NR). PRE was defined as $\geq 50\%$ resolution of the number of symptoms; PR was defined as less than 50% resolution of the number of symptoms. A secondary end point was time from initiation of the reversal agent until CR.

One hundred and fifty-two patients (63%) developed symptoms suggesting an indication for reversal. The most common symptoms were, in decreasing order, dyspnea, gastrointestinal discomfort, headache, and flushing. Of the 152 patients who received a reversal agent, 129 (85%) had complete response, 15 (10%) PRE, 6 (4%) PR, and 2 (1%) NR. In the aminophylline group (53 patients), 46 (87%) had CR, 7 (13%) had PRE, and no patients had PR or NR. Of the 67 patients in the IV caffeine group, 58 (87%) had CR, 6 (9%) had PRE, and 3 (4%) had PR. In the oral caffeine group of 32 patients, 25 (78%) had CR, 2 (6%) had PRE, 3 (9%) had PR, and 2 (6%) had NR. Comparing the rates of complete response of IV aminophylline (87%), IV caffeine (87%), and oral caffeine (78%), no statistical difference was present between the three groups. Of note, the combined endpoint of CR and PRE was similar between IV aminophylline and IV caffeine (100% and 96%, respectively, $P = .12$); IV aminophylline was superior to oral caffeine (100% and 84%, respectively, $P = .003$) and there was a trend that IV caffeine was superior to oral caffeine (96% and 84%, respectively, $P = .057$). There was no statistical difference in the duration of symptoms between the groups but a trend toward a more rapid response to the 30- to 60-second infusion of aminophylline (149 ± 118 seconds) compared to the 3- to 5-minute infusion of caffeine (162 ± 135 seconds) and of IV caffeine over a caffeinated beverage (186 ± 197 seconds). Nineteen of the 37 patients (37%) in the oral caffeine group crossed over to the IV caffeine. Women required reversal more frequently than men ($P < .001$) and were more likely to have an IR ($P = .016$).

A limitation of the study was the lack of a placebo group, which would allow the determination of the duration of adverse effects of regadenoson without intervention. In their evaluation of the duration of the

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$$\begin{aligned} \text{Cardiac Output} &= \text{Heart rate} \times \text{Stroke Volume} \\ \text{Stroke Volume} &= \text{End-diastolic volume} - \text{End-systolic volume} \\ \text{To simplify calculations, assumed a mean stroke volume of 70cc/beat} \\ &\text{and a heart rate of 87 bpm one minute after regadenoson.} \\ \text{Cardiac Output} &= 87 \text{ beats/min} \times 70 \text{ ml/beat} = 6090 \text{ ml min} (\approx 6.1 \text{ L/min}) \\ \text{Assumed total blood volume to be 5 L} \\ \text{Circulation time} &= (\text{total blood volume} \div \text{Cardiac Output}) \times 60 \text{ sec/min} \\ &= (5 \text{ L} \div 6.1 \text{ L/min}) \times 60 \text{ sec/min} = 49.2 \text{ sec} \\ \text{Thus, percent extraction by the myocardium at 1 sec} &= \\ (\text{Extraction fraction}) \div \text{Circulation time} &= \text{Percent extraction at 1 sec} \\ \text{Therefore, percent extraction by the myocardium at 1 min} &= \\ (\text{Percent extraction at 1 sec}) \times 60 \text{ sec} &= \text{Percent extracted at 60 sec (1 min)} \\ \text{Example, Extraction percent at one min} &= (60\% \times 60 \text{ sec}) \div 49.2 \text{ sec} = 73.2\% \end{aligned}$$

Fig. 1. Calculation of percent extracted by the myocardium per unit time using Cardiac Output/ Circulation time. *L* liters, *sec* seconds, *min* minute.

hemodynamic effect of 0.4 mg of IV regadenoson in eight subjects, Lieu et al found that regadenoson increased coronary blood velocity to a mean peak of 3.1 ± 0.5 times baseline at 1 to 2 minutes.³ Velocity gradually decreased to twice baseline by 10 minutes. Using increased coronary velocity as a surrogate for vasodilation in other arteries, some degree of headache and flushing could be expected to last ≥ 10 minutes. The three-compartment half-life model elucidated by Gordi et al^{4,5} makes the duration of other adverse effects such as gastrointestinal distress difficult to estimate based upon pharmacodynamics.

A key issue is how long to wait before administering a reversal agent in patients who develop symptoms. In a randomized trial of 207 pts, Tejani et al⁶ found 200 to 400 mg of oral caffeine in pill form administered 90 minutes prior to regadenoson to substantially decrease defect size. Thus, adequate time should be allowed for the radiotracer to be taken up by the myocardium prior to reversing the effect of regadenoson.

Using the assumptions of an extraction fraction of Tc-99 m of 60%, a stroke volume of 70 cc, a heart rate of 87 bpm (1 minute post regadenoson), and a blood volume of 5 L, we calculated that the estimated percent extraction of a Tc-99 m radiotracer by the myocardium at 1, 2, 3, 4, and 5 minutes would be 73.2, 92.8, 98.1, 99.5, and 99.9%, respectively (Fig. 1). Duran and colleagues choose to reverse at 4.5 minutes,¹ at which time extraction would be expected to be 99.7%.

One key factor affecting drug/receptor interaction is the affinity of reversal agents (antagonists) relative to the agonist for the particular receptor. With respect to competitive binding, it is important to know the affinity of a drug to the receptor that can be determined by looking at the K_i or inhibitory constant. The K_i is defined as the amount of a drug required for 50% maximum activity at specific receptor. Fredholm et al⁷ classified adenosine receptors into the distinct subtypes A1, A2a, A2b, and A3. Regadenoson has a selective affinity for the A2a receptor with a K_i at 1269 nM and acts as an agonist.⁸ Competitive antagonists of the A2a receptor, caffeine and theophylline (the active ingredient of aminophylline), have K_i 's 5 to 7 times higher, 9560 ± 670 nM⁹ and 6700 ± 320 nM,¹⁰ respectively. Each of these analyses was performed in HEK-293 human cell cultures. Following injection of the agonist regadenoson, an injection of a competitive antagonist such as caffeine and theophylline will compete for the A2a receptor based on their affinities and concentrations. Given the lower K_i , and thus greater affinity of regadenoson, ≈ 5 times more molecules of theophylline and ≈ 7 more caffeine molecules would be needed to produce 50% of the maximum effect on the A2a receptor compared to regadenoson.

Knowledge of the molecular weight and dose allows one to calculate the number of molecules competing for the A2a receptor (Fig. 2).

Based on the calculations shown in Fig. 2, we found that ≈ 435 times more aminophylline molecules are

$$\begin{aligned} \text{Number of molecules} &= \text{number of moles} \times \text{Avogadro's constant } (6.0221409 \times 10^{23}) \\ \text{Number of moles} &= \text{mass(g)} \div \text{molar mass(g/mol)} \end{aligned}$$

A) IV Aminophylline (molar mass of 420.427 g/mol):
Theophylline (molar mass of 180.164 g/mol):
Aminophylline is composed of 80% Theophylline and 20% Ethylenediamine
Assume dose of 100 mg (0.01g) of aminophylline = 80 mg (0.08 g)
of theophylline and 20 mg Ethylenediamine
Number of moles of theophylline = $0.08 \text{ g} \div (180.164 \text{ g/mol}) = 4.44 \times 10^{-4} \text{ moles}$
Number of molecules of theophylline = $4.44 \times 10^{-4} \text{ moles} \times \text{Avogadro's constant}$

B) IV Caffeine Citrate (molar mass of 386.314 g/mol):
60 mg (0.06 grams)
Number of moles of cCaffeine Citrate = $0.06 \text{ g} \div (386.314 \text{ g/mol}) = 1.55 \times 10^{-4} \text{ moles}$
Number of molecules = $1.55 \times 10^{-4} \text{ moles} \times \text{Avogadro's constant}$

C) IV Regadenoson (molar mass of 390.354 g/mol):
0.4 mg (0.0004 grams)
Number of moles = $0.0004 \text{ g} \div (390.354 \text{ g/mol}) = 1.02 \times 10^{-6} \text{ moles}$
Number of molecules = $1.02 \times 10^{-6} \text{ moles} \times \text{Avogadro's constant}$

$$\begin{aligned} \text{Relative ratio of molecules} &= \frac{\text{Number of moles of A} \times \text{Avogadro's number}}{(\text{Number of moles of B} \times \text{Avogadro's number})} \\ &= \frac{\text{Number of moles of A}}{\text{Number of moles of B}} \end{aligned}$$

Ratio of molecules of IV aminophylline to regadenoson = 435
Ratio of molecules of IV Caffeine citrate to regadenoson = 152

Fig. 2. Calculation of the number of molecules of each aminophylline, caffeine, and regadenoson.
Mol mole, g grams.

injected in a dose of 100 mg IV aminophylline relative to the number of regadenoson molecules injected in a 0.4 mg dose of regadenoson and a dose of 60 mg of IV caffeine citrate includes ≈ 152 times more caffeine molecules relative to regadenoson molecules (not accounting for half-lives). Based on the ≈ 5 times greater affinity of regadenoson for the A2a receptor relative to aminophylline, one can divide 435 by 5 ($=87$) to obtain a measure of the ability of the agents to compete for the receptor in the concentrations of molecules available. Thus, for aminophylline there are ≈ 435 more molecules than regadenoson and given their relative affinities this is equivalent to ≈ 87 times more molecules. Such a substantial difference explains the rapidity and effectiveness of reversal of the hemodynamic effects and symptoms with aminophylline.

As regadenoson has an affinity to the A2a receptor ≈ 7 times that of caffeine, one can divide the ≈ 152

times greater number of molecules of caffeine available than regadenoson, yielding the equivalent of ≈ 22 times more molecules. This is consistent with the substantial reversal of symptoms observed by Doran et al.¹

Oral caffeine was the third agent evaluated by Doran et al;¹ however, ingested dosages were not accurately measured. Blanchard et al¹¹ found that a 5 mg/kg oral dose of caffeine (350 mg for a 70 kg person) was absorbed as rapidly with comparable bioavailability compared to a IV caffeine infusion of 210 mg caffeine infused over 30 minutes.

Given the pharmacodynamics of regadenoson, aminophylline, and caffeine, when is the optimal time to administer a reversal agent following regadenoson? Reversal was used only 3% of the time in the pivotal trials,¹² but some laboratories reverse nearly all patients. For example, Doukky and colleagues demonstrated a substantial decrease in gastrointestinal, headache, and

other adverse events with the routine use of IV aminophylline.¹³ Doran et al used a low threshold for reversal in their study, reversing 63% of patients.¹ Most labs choose a higher threshold and reverse a much lower percentage of patients. If a patient is reversed, we recommend waiting 3 minutes following radiotracer administration. In patients with a normal cardiac output, one would expect $\approx 98\%$ of Tc-99 m to be extracted by the myocardium at that time. If poor cardiac output is suspected, one could delay reversal for another minute. If urgent reversal is required for patient safety, reversal should occur at the time of concern. However, if a reversal agent is administered prior to 2 minutes, the sensitivity of the test may be compromised.

This area of research could be further explored in a follow-up multicenter study with a larger patient sample size and a study design that includes a placebo arm, allowing for rescue IV aminophylline or IV caffeine for serious adverse effects. For an oral caffeine arm, careful measurement of the amount of oral caffeine consumed would be helpful. A quantitative patient satisfaction Likert scale could also allow a more granular comparison of the reversal agents.

Fortunately, IV caffeine is generally available commercially and inexpensive. The University of Rochester cost for a 3-mL vial of 60 mg of IV caffeine citrate is \$5.64.¹⁴ Aminophylline is also inexpensive, \$9.81 for a 10-mL vial containing 250 mg.¹⁴

What can we conclude from this pivotal contribution of Doran and colleagues? (1) Based on the results of the trial, buttressed by the magnitude of the difference in caffeine to regadenoson molecules reviewed above, 60 mg of IV caffeine over 3 to 5 minutes is an effective agent in the reversal of regadenoson and is essentially equivalent to IV aminophylline. (2) For mild symptoms, oral caffeine is a good first choice, reserving IV aminophylline or caffeine if symptoms do not resolve or if gastrointestinal or other symptoms preclude the ability to drink a caffeinated beverage.

Disclosures

Aaron F. Jolly, MD, has no disclosures. Gregory S Thomas, MD, MPH, is a member of the speakers bureau of Astellas Pharma US.

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