Evaluation of Intravenous Infusion Systems for Adenosine

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Adenosine is used routinely in cardiac perfusion imaging in lieu of exercise stress to enhance coronary blood flow. Since it is a potent drug, intravenous (IV) infusion of adenosine must be carefully controlled to provide optimal pharmacologic effect and minimal adverse effects. There has been particular concern about a sudden increase in adenosine delivery at the time of radiotracer administration which has prompted recommendations for using separate IV infusion sites or double lumen IV catheter sets. To evaluate infusion control, five IV infusion systems were evaluated for their ability to accurately deliver adenosine with co-administration of a radiopharmaceutical, such as thallium-201 (^{201}Tl) into the infusion line. A decrease in adenosine infusion occurred with the Buretrol gravity drip system when ^{201}Tl was injected into the infusion line. A temporary, intermittent decrease of adenosine infusion also occurred with the IMED infusion system because of its pumping mechanism. No significant change in adenosine infusion occurred with either the Harvard or Medfusion syringe pumps or with the IVAC infusion pump. No significant increase or bolus effect of adenosine administration occurred with any of the infusion systems.

Adenosine is an endogenous nucleoside involved in the autoregulation of coronary blood flow. An injectable form of adenosine (Adenocard, 3 mg/ml, 2 ml) is available for the treatment of cardiac conduction abnormalities. In nuclear medicine, adenosine may be used in lieu of exercise to increase coronary blood flow during cardiac perfusion imaging with thallium-201 (^{201}Tl) chloride or one of the technetium-99m (^{99m}Tc) myocardial perfusion agents. Typically, adenosine is administered at a dosage rate of 140 μg/kg/min for 6 min; the ^{201}Tl is administered at 3 min into the infusion (*1*). The short duration of adenosine's pharmacologic effect, due in part to a plasma half-life of <10 sec. (*2*), necessitates administration of the radiopharmaceutical during the adenosine infusion.

Recommendations proffered in the literature (*3,4*) note that adenosine and the radiopharmaceutical should be administered via separate intravenous (IV) sites. The reason given is that radiopharmaceutical administration into the adenosine infusion line may temporarily alter its rate of infusion, causing an increase or bolus effect in the amount of adenosine infused. Such concern is naturally warranted since adenosine is quite potent and possesses the ability to cause atrioventricular block if rapidly infused. Additionally, its short half-life may cause plasma levels to fall below those required for full pharmacologic effect, if the infusion is interrupted for a short period of time, such as when the radiotracer is administered.

From a technical viewpoint, instituting one IV line instead of two would be more convenient, less costly, reduce the patient preparation time, and cause fewer problems associated with placement of the blood pressure cuff. Therefore, the purpose of this study was to substantiate the validity of the previous cautions by determining whether an alteration of adenosine infusion actually occurs during co-administration of a radiopharmaceutical into the infusion line.

MATERIALS AND METHODS

Five infusion systems were evaluated. They were a gravity infusion system (Buretrol, Travenol Labs., Deerfield, IL), two syringe pumps (Harvard Apparatus Co., Millis, MA, Model 903, and Medfusion Inc., Deluth, GA, Models 2001 and 2010), and two volumetric infusion pumps (IVAC-560, IVAC Corp., San Diego, CA and IMED-980C, IMED Corp., San Diego, CA). These systems, or ones similar in function, are usually available in hospitals for intravenous infusion.

The Buretrol is a gravity drip system consisting of a drip chamber and an IV line of ~15-ml internal volume, connected to a fluid reservoir that can hold 150 ml of drug solution. The Harvard pump is a mechanically driven system that delivers drug solution from a syringe via an IV line to the patient. The IV line used with the Harvard pump was either a standard IV extension set (33-in./5.5-ml, # BC596, Codan Medlon Inc., Burbank, CA) or microbore IV sets (24-in./0.28-ml, # 48-11, International Medical Industries, Watertown, MA or 60-in./1.0 ml, # 53-60-35 and 60-in./0.28-ml, # 53-36-40, Medfusion Inc., Duluth, GA). The infusion rates of the Buretrol and Harvard pump were calibrated using a stopwatch and graduated cylinder.

The IVAC pump utilizes a linear peristaltic mechanism in its pumping chamber. The infusion line from the fluid reser-

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voir to the patient is positioned in the pumping chamber between a stationary plate and a row of moving "fingers," which sequentially press the tubing against the plate. The resultant "milking" motion propells fluid through the infusion line. The IMED pump utilizes a piston mechanism between the drug reservoir and the patient to pump fluid through the infusion line. The internal volume of the IV set was ~15 ml for these two pumps. The Medfusion syringe pump is programmable to accept various brands and sizes of syringes. For this study, a 60-ml, B-D syringe and the microbore IV sets cited above were used. With the IVAC, IMED, and Medfusion pumps, a wide range of flow rates were selected using digital electronic controls. Each of these pumps was checked for accuracy using a graduated cylinder and stopwatch.

The outlet of each IV infusion line was equipped with a T-connector infusion set (# MX453-L, Medex Inc., Hilliard, OH) and a 22-gauge IV catheter. The infusion setup for a syringe pump is shown in Figure 1. A solution of ^{99m}Tc sodium pertechnetate, 0.1 μCi/ml, was prepared to simulate the adenosine infusion. Each system was filled with the pertechnetate solution and tested at three infusion rates: 3, 6, and 9 ml/min. These rates were chosen because they span the expected range of adenosine infusion rates used in our cardiac imaging laboratory, where adenosine is diluted with saline to a concentration of 1.5 mg/ml. The Medfusion pump was tested at flow rates of 1.7, 3.8, and 5.9 ml/min to span the infusion range of undiluted, i.e., 3 mg/ml, adenosine. Aliquots, equivalent to a 10-sec. infusion time per aliquot, were collected in test tubes as a control. Five aliquots at each infusion rate were collected for each system. To measure the effect of radiopharmaceutical co-administration into the infusion line, the above sampling scheme was repeated, except that 1 ml of water (simulating the radiopharmaceutical) was injected into the T-connector port during the collection of each aliquot. (The effect of larger volumes of water injected was also studied and is discussed below.) The injection time was 4 to 5 sec. Prior to sample counting in a scintillation well counter, control samples were created, adding water to match the volume of the experimental samples collected at each infusion rate.

RESULTS

The net counts per minute for control and experimental samples at each infusion rate were averaged and compared and are shown in Table 1. From this data, it is evident that the difference in mean counts between control samples (without co-injection of simulated radiopharmaceutical) and experimental samples (with co-injection of simulated radiopharmaceutical) was not significantly different for the automated infusion systems. Only the gravity fed (Buretrol) delivery system produced a significant difference between the control and experimental samples: the mean count decreased in the experimental sample. Although there was no evident difference seen for the IMED system, a property of its infusion mechanism makes its choice questionable for adenosine infusion, as discussed below.

DISCUSSION

To choose an accurate infusion system one must evaluate the operating characteristics of each system. The infusion rate of the Buretrol system is controlled by a roller clamp in the IV line. Because it is a gravity fed system, the rate is also affected by the volume and height of the fluid reservoir, i.e., hydrostatic pressure. Thus, it is difficult and overly time consuming to set a specific rate accurately. Additionally, the rate of flow of a low pressure gravity system is most likely to

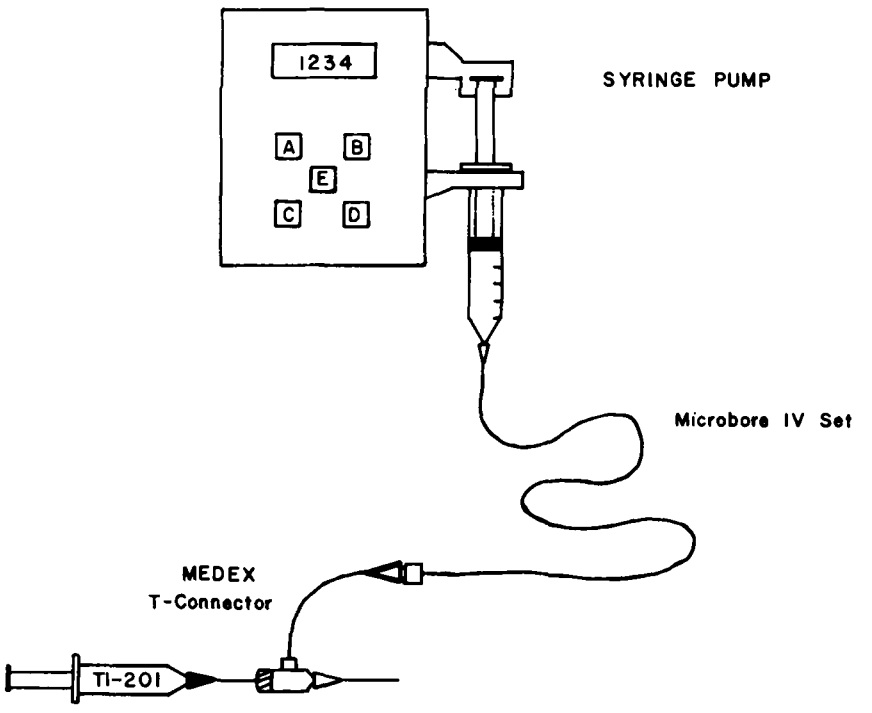

FIG. 1. Adenosine infusion system.

TABLE 1. Comparison of Adenosine Infusion Systems

System		Mean Counts per Minute at Infusion Rates		
		3 ml/min	6 ml/min	9 ml/min
Buretrol	A	63,046 (863)	111,337 (4137)	145,836 (3939)
	B	17,404 (2597)	60,228 (2832)	91,972 (1990)
% difference		−72.39	−45.90	−36.93
IVAC	A	33,701 (1012)	57,899 (685)	75,337 (1555)
	B	34,285 (729)	58,772 (889)	74,979 (1045)
% difference		+1.73	+1.51	−0.48
IMED	A	26,816 (580)	48,739 (562)	63,925 (957)
	B	26,945 (248)	48,490 (495)	63,591 (1934)
% difference		+0.48	−0.51	−0.52
Harvard Pump	A	53,705 (2270)	94,757 (1647)	122,341 (658)
	B	53,199 (2055)	93,936 (987)	121,506 (2353)
% difference		−0.94	−0.87	−0.68
		1.7 ml/min	**3.8 ml/min**	**5.9 ml/min**
Medifusion Pump	A	18,109 (1230)	37,387 (870)	50,809 (486)
	B	18,367 (1270)	36,377 (645)	50,944 (607)
% difference		+1.42	−2.70	+0.27

(A) without and (B) with 1 ml water injected into infusion line T-connector. Mean of 5 determinations and (s. d.).
Percent difference = (B − A/A) × 100.

be temporarily altered when drugs are injected into the line. Such was evident in this study, when a substantial decrease in the amount of infused radioactivity occurred during the water injection. The decrease was inversely related to infusion rate, indicating that backpressure created in the IV line during injection was the probable cause.

To evaluate this further, the effect of the volume of radiopharmaceutical injected on infusion rate was studied. Experiments were repeated with the Buretrol and the Harvard pumps at the 6 ml/min infusion rate, except that 2 ml or 3 ml of water were injected over 8-10 sec during sample collection. The mean counts per minute infused decreased 2% with the Harvard pump and 47% with the Buretrol pump when 2 ml were injected and decreased 5% with the Harvard pump and 73% with the Buretrol pump when 3 ml were injected. Thus, the increased pressure created when larger volumes were injected over the same time frame caused injected solution to back up in the gravity-fed infusion line, significantly decreasing the amount of activity infused

To evaluate whether the site of water injection into the line affected infusion rate, a repeat experiment was conducted at the 9 ml/min rate, with water injected into a port between the T-connector and the Buretrol. This experiment produced a 45% decrease in the amount of radioactivity infused compared to a 37% decrease observed at this same infusion rate with water injected into the T-connector port. Thus, no augmentation of adenosine infusion occurred with the gravity system, regardless of where the radiopharmaceutical was injected into the line, but a definite decrease in adenosine infusion occurred during the time of injection.

Two principal factors can affect the rate of IV drug (adenosine) administration during co-administration of a second drug (^{201}Tl) into the line: internal pressure of the infusion system and flow restriction of the cannula at the venipuncture site. There was no significant change in the amount of radioactivity infused during co-administration of 1 ml of water into the infusion line with any of the pump systems tested. A positive internal pressure, such as that provided by an infusion pump, will resist better the backflow created by an IV bolus of ^{201}Tl than will a gravity fed system. The smaller decrease seen (2% to 5%) with the Harvard pump, when 2-ml to 3-ml volumes were injected, indicates that positive pressure systems are not likely to have any significant effect on the amount of adenosine infused when doses of ^{201}Tl are administered into the IV line.

Regarding cannula flow restriction, if the bore of the IV catheter is large enough to accommodate both the flow of infused adenosine and the increased flow caused by co-administration of ^{201}Tl, no significant change in the net amount of adenosine infused should occur. In this experiment, a small bore (22-gauge) IV catheter was used. Since it did not demonstrate any significant restriction to flow, a larger bore IV catheter should perform equally as well. We have had no clinical problems resulting from the small volume of adeno-

sine pushed in from the IV catheter chamber and lumen in front of the tracer volume in over 15 mo of using this technique with the Harvard syringe pump.

In the routine care of patients on parenteral fluids, it is not uncommon for the IV line to be crimped off temporarily while medication is injected into the IV line. While this practice is satisfactory with gravity infusion systems, it would create a pressure buildup in a pump driven infusion system. In such situations, when the crimp is released, a rapid infusion of IV solution would occur in response to the pressure. If adenosine were the infusion solution, this practice would likely create a bolus injection of adenosine. As shown in this study, such a practice is not necessary with pump driven infusion systems and should not be employed.

It is important to note an operational characteristic of the IMED pump. The pump provides a fixed rate of flow while its cylinder is being emptied, but the infusion stops temporarily for about 8 sec (~1 half-life of adenosine) while the cylinder is being refilled. The cylinder has a volume of 4 ml, so that at an average infusion rate of 4 ml/min, the patient will not receive the drug for 8 sec of every min of infusion. During a 6-min infusion of adenosine at this rate, five refills or five breaks in adenosine infusion would occur. This intermittent cessation of flow would not be a significant problem for most large-volume IV drugs, but might present a problem for short-acting drugs such as adenosine.

During the treatment of hospitalized patients, large-volume IV fluids without specific medications are routinely administered into peripheral veins by gravity drip systems. Under these circumstances, the small changes in flow rate that may occur as solution is depleted are not critical to patient care. However, when highly accurate administration of a potent drug such as adenosine is required, a pump infusion system should be used. The two syringe pumps (Harvard and Medfusion) evaluated in this study and the IVAC peristaltic pump provided uninterrupted flow of fluid at the preset infusion rate and are recommended for achieving accurate infusion of adenosine.

A disadvantage of the Harvard pump is that it has to be calibrated for the particular syringe size being used. However, once calibration is established, routine use is simple. With our use of this pump, we have prepared a chart, listing adenosine dosage and infusion rates as a function of patient weight in 5-lb increments. A programmable syringe pump is a more desirable alternative because infusion parameters, such as syringe size, dosage, and infusion rate, can be dialed in for a specific patient's weight. These pumps are also much smaller, can be hung on an IV pole, and may have battery power.

From an economic standpoint, another factor to consider during adenosine infusion is the volume of the infusion line. A standard 30-in. infusion set has an internal volume of about 5 ml. This volume of adenosine will end up being a costly (~$40) waste because it is not infused during the procedure. Many IV lines have larger internal volumes and would generate higher costs. This is a disadvantage of the IVAC and IMED infusion pumps. Waste can be minimized by diluting the adenosine in saline or by using microbore IV tubing, which has minimal internal volume. However, if one chooses to use microbore sets, the user should be aware that the small internal diameter of this tubing creates increased resistance to flow and may not be suitable for use at high infusion rates.

In this study, the Harvard pump and the Medfusion pump provided good results with standard IV tubing and with the 24-in./0.28-ml and 60-in./1.0-ml internal volume microbore sets. At the high flow rates needed for adenosine infusion, the 60-in./0.28-ml volume microbore set created too much resistance for the Harvard pump, causing it to skip during infusion, and for the Medfusion pump, causing its occlusion alarm to sound.

An advantage of the Medfusion 2010 pump is that the infusion rate is automatically set by the pump once the drug dosage rate, in μg/kg/min, and patient weight are programmed. The maximum flow rate of the Medfusion pump with a 60-ml B-D syringe is 355 ml/hr (5.9 ml/min). This necessitates the use of undiluted adenosine, i.e., at 3 mg/ml strength, and allows delivery of a dosage of 140 μg/kg/min to patients weighing up to 279 lb. A heavier patient would require use of the Harvard or IVAC pump, both of which can achieve higher infusion rates.

The gravity infusion system and the IMED infusion pump are not recommended systems for adenosine infusion because they cause transitory decreases in the amount of adenosine infused. These decreases may cause a reduction of adenosine's pharmacologic effect on coronary blood flow because of adenosine's short plasma half-life. Wilson et al. (*5*) measured the effects of adenosine on human coronary circulation. Their findings indicate that maximal coronary vasodilation is achieved at an infusion rate of 140 μg/kg/min. However, at lower infusion rates (70–100 μg/kg/min), coronary blood flow velocity often rises and falls in a cyclic pattern with a cycle length of about 30 sec.

Adenosine's short half-life essentially means that its distribution is described by a one-compartment model and follows first-order kinetics. Thus, if adenosine infusion is temporarily stopped for the duration of 1 half-life, e.g., ~10 sec., its plasma level will be cut in half and will require ~1 min (i.e., 5–6 half-lives) to reach original levels again after infusion resumes. If cessation of flow occurs soon after ^{201}Tl is injected, its distribution in the heart may be affected by altered blood flow and result in false-normal findings. Due to these possible effects, it is best to choose an IV infusion system that guarantees consistent adenosine delivery throughout the procedure.

CONCLUSION

The results of this study show that co-administration of ^{201}Tl into the adenosine infusion line does not cause a significant sudden increase (bolus effect) in the amount of adenosine administered, under the conditions of this study. Use of a gravity drip system of adenosine administration is not recommended because a decreased amount of adenosine infused will occur during ^{201}Tl administration into the line. The IMED system is not recommended because it temporarily

stops adenosine infusion during its normal operation, and the plasma level of adenosine may not return to its original level for ~1 min. A recommended system is an IV syringe pump fitted with a microbore infusion set having an injection port close to the IV site (Fig. 1). Such a system will allow the simplicity of a single venipuncture injection site, essentially direct IV injection of ^{201}Tl, no significant alteration of the amount of adenosine infused, and minimal waste (reduced cost) of adenosine.

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REFERENCES

1. Coyne EP, Belvedere DA, Vande Streek PR, et al. Thallium-201 scintigraphy after intravenous infusion of adenosine compared with exercise thallium testing in the diagnosis of coronary artery disease. *J Am Coll Cardiol* 1991;17:1289–1294.
2. Rubio R, Berne RM, Katori M. Release of adenosine in reactive hyperemia of the dog heart. *Am J Physiol* 1969;216:56–62.
3. Boyce TM, Guidry GW, Mahmarian JJ, et al. Adenosine cardiac imaging. *J Nucl Med Technol* 1991;19:203–209.
4. Alazraki N. Nuclear imaging of the cardiovascular system. In: Elliott LP, ed. *Cardiac imaging in infants, children and adults.* Philadelphia, PA: J.B. Lippincott; 1991:41–55.
5. Wilson RF, Wyche K, Christensen BV, et al. Effects of adenosine on human coronary arterial circulation. *Circulation* 1990;82:1595–1606.