The Delivery of Drugs to Patients by Continuous Intravenous Infusion: Modeling Predicts Potential Dose Fluctuations Depending on Flow Rates and Infusion System Dead Volume

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IV drug infusion has the potential for dosing errors, which arise from complex interactions between carrier flows and the infusion set dead volume. We computed the steady-state mass of drug stored in the infusion set dead volume, using phenylephrine as a model compound. The mass of drug in the dead volume increases with stock drug concentration and desired dose but decreases with carrier flow rate. We also modeled the dynamic perturbations in drug delivery when a carrier is abruptly stopped. Rapid initial carrier flow rates lead to greater depression in drug delivery rate after carrier flow ceases. Rapid drug infusion rates lead to faster restoration of desired drug delivery. Finally, the time to reach a new steady-state after a change in drug delivery or carrier rate was computed. This time is longest for large stock-drug concentrations, larger dead volumes, and slower final carrier rates. These computations illustrate that (a) the dead volume may contain a large mass of drug available for inadvertent bolus, (b) cessation of carrier flow can profoundly reduce drug delivery, and (c) after a change in carrier flow or drug dosing, a significant lag is possible before drug delivery achieves steady state. Although computed for phenylephrine, the concepts are generic and valid for any drug administered by IV infusion.

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A 65-yr-old man underwent colectomy with a general anesthetic combined with a T8-9 epidural. Bupivacaine 0.5% was infused in the epidural at 8 mL/h throughout the case, and his arterial blood pressure (BP) was supported with an infusion of phenylephrine delivered by a syringe pump through a peripheral IV. After uneventful emergence and tracheal extubation, the patient was rapidly transported to the postanesthesia care unit (PACU) to accommodate an incoming emergency procedure. His vital signs leaving the operating room (OR) were heart rate of 89 bpm and BP of 151/70 mm Hg. Because an IV pole could not be found, the IV bag was placed on the stretcher. The phenylephrine infusion continued. Upon arrival in the PACU, the IV bag was suspended and flow resumed. The first vital signs measured in the PACU were heart rate of 42 bpm and BP of 250/149 mm Hg. Hemodynamics returned to normal after cessation of the phenylephrine infusion and the patient did well.

Vasoactive, antidysrhythmic, inotropic, and sedative and analgesic drugs are often infused into surgical patients under anesthesia in the OR or critically ill patients in the intensive care unit (ICU). Precise control of the delivery of powerful cardio-stimulatory drugs such as epinephrine, vasopressors such as phenylephrine, or vasodilators such as nitroglycerin or sodium nitroprusside is essential to achieve desired therapeutic end-points and to avoid deleterious fluctuations in the patient’s clinical condition. The basic components of an infusion system include (a) a reservoir of the drug to be infused, (b) a device to control the rate of drug egress from the reservoir, and (c) a tubing system connecting the rate control device to the fourth component, which is the vascular access catheter. A fifth component, a mainline or carrier flow, may also appear in some clinically used infusion systems (1,2). In this case, the drug infusion joins the mainline or carrier flow at a junction point upstream from the patient.

Frequently, pumps are used to drive the delivery of IV infused drugs in a controlled fashion. Previous studies have examined pump performance characteristics (3–11). Experimental data demonstrated that cyclic changes in pump output, determined by the
mechanical features of the pumps, correlate with hemodynamic fluctuations (3,5,6,8). Consequently, considerable attention has been directed towards optimizing pump design to reduce the likelihood of clinically significant fluctuations in drug delivery (1,2).

Less attention has been paid to other components of the infusion system. Whereas drugs may be infused directly into the patient, limited vascular access or the need to simultaneously provide two or more IV fluids means that drug infusions may join a mainline carrier infusion. Many patients are intolerant of fluid loads (12,13). Thus, at some institutions the amount of fluid infused into patients has been reduced by increasing the stock concentration of drugs (14). Consequently, the desired mass (dose) of drug is delivered in a small volume. Whereas the patient potentially benefits from a reduced volume load from concentrated stock drug, clinical experience suggests the possibility of an enhanced risk for unplanned changes in drug delivery (14). This risk can be attributed to unrecognized reservoirs of concentrated drug within the IV infusion set. These changes may have significant clinical consequences, such as profound vasoconstriction, vasodilation, or loss of inotropic support. Indeed, in the clinical vignette described above, a real case managed by experienced clinicians, we suspect that the phenylephrine infusion driven by the syringe pump accumulated in the IV tubing when the main IV flow stopped during the transport interval. When the IV bag was resuspended on a pole in the PACU, the patient received a large bolus of vasopressor resulting in the episode of hypertension.

We have previously described and experimentally validated theoretical models to characterize the dynamics of drug delivery by IV infusion (15). Factors anticipated to affect drug delivery include the flow rate of the mainline or carrier infusion (Qc), the flow rate of the drug infusion (Qd), and the infusion system dead volume (V) defined as the volume between the reservoir of the dead volume and use the previous models to predict changes in drug delivery depending on alterations in carrier flow and infused drug dose rate. The findings extend the previous work by illustrating in greater detail the possibilities for interplay among Qc, Qd, and V, and the magnitude of perturbations in drug delivery when these factors are altered.

**Methods**

All of the following equations are generic, applicable to any infused drug, and assume an infusion system architecture in which a flow of drug (‘piggyback’) joins a carrier. A joining point might be at the side port of an IV extension set or a stopcock. At steady-state, the concentration of the drug throughout the dead volume (Cv) is given by the dilution of the stock-drug concentration (Cd) by the carrier flow rate (Equation 1).

\[
C_v = \frac{Q_d}{Q_d + Q_c}
\]

Qd is the drug infusion rate (I), in units of mass per unit time, divided by Cd. Substituting this relationship into Equation 1 shows:

\[
C_v = \frac{I}{I/C_d + Q_c}
\]

The total mass of drug in the dead volume (Mv) is a function of the dead volume and the concentration of drug in the fluid path.

\[
M_v = V \cdot C_v = \frac{V \cdot I}{I/C_d + Q_c}
\]

This would be the mass of drug available for a bolus, should the carrier rate abruptly increase, or if there is an upstream ‘push’ of fluid (e.g., another drug). The potential drug bolus residing within the reservoir of the infusion system dead volume was calculated as a function of drug infusion dose (I), with varying Qc, Cd, and V.

In clinical practice, carrier flows sometimes stop inadvertently, as when a bag of crystalloid empties unnoticed. In this scenario, the rate of drug delivery into the patient initially decreases as the reservoir of diluted drug in the dead volume now infuses at a much slower rate, given by:

Initial Delivery rate after carrier ceases =

\[
Q_dC_v = \frac{I^2}{I + Q_cC_d}
\]

The return of drug delivery to the planned steady-state while the carrier infusion is off was previously described by two models of crystalloid and drug flow within V (15). These models make divergent assumptions about the mixing of drug infusion and carrier flows. The plug-flow model assumes that the streams of drug and carrier mix perfectly at the point where they meet. The mixed fluid in this model is assumed to travel downstream as a plug. Changes in the rate of drug infusion propagate along the fluid path according to the total flow rate, the sum of the carrier and drug flow rates. After a change in either the carrier flow or the drug infusion flow rate, the time to achieve
the planned steady-state delivery of drug is one time constant ($\tau$):

$$
\tau = \frac{V}{Q_d + Q_c} = \frac{V}{I/C_d + Q_c}
$$

At the other extreme, the well-mixed model assumes that the concentration of drug everywhere in the dead volume is uniform (15). After a change in either the drug infusion or carrier flow rate, the time to achieve the planned steady-state delivery of drug is approximately three time constants, threefold more than in the plug-flow model (15). The equation describing drug delivery to the patient after the carrier is halted appears in the Appendix.

We used these equations to predict the potential bolus of drug stored in the reservoir of the dead-volume (Mv; Fig. 1). We then explored the consequences of abruptly turning off a carrier by calculating the drug delivery rate just after carrier flow ceases (Fig. 2) and the time course for reestablishing steady-state as predicted by the well-mixed and plug-flow models (Figs. 3 and 4). Finally, we generalize the interaction between the carrier flow and the dead volume by calculating the time to achieve steady-state after a change in either flow rate (Fig. 5). Computations covered a range of drug infusion doses, carrier flows, stock-drug concentrations, and dead volumes. Major assumptions in these calculations are that the pump driving the drug infusion operates without fluctuations and that any carrier flow is continuous without any fluctuations in rate unless specified.

Phenylephrine is frequently used in the OR or the ICU and is chosen as a representative infused vasovactive drug. The principals should apply, however, to any drug delivered by continuous IV infusion, including vasopressors such as epinephrine or norepinephrine, vasodilators such as nitroglycerine or sodium nitroprusside, analgesics such as remifentanil or fentanyl, or sedative-hypnotic drugs including propofol.

**Results**

The concentration of a drug in the dead volume of an infusion system at steady-state depends on the flow rate of the carrier fluid diluting the infused drug. For a given planned drug infusion rate, the dead volume drug concentration decreases as the carrier rate increases (Equation 2). At slow carrier rates ($I/C_d > Q_c$), the stock concentration of drug is only slightly diluted. At steady-state there is a predictable mass of drug in the dead volume (Fig. 1A). For example, at a planned phenylephrine infusion dose of 100 $\mu$g/min, a dead volume of 2 mL, a stock concentration of 1.2 mg/mL, and a carrier rate of 10 mL/h, there are 800 $\mu$g of phenylephrine contained in the dead volume reservoir at steady-state. Alternatively, if the carrier flow rate was 100 or 500 mL/h, the drug stored in the dead volume would be 114 or 24 $\mu$g, respectively. Conversely, if the infusion ran without a carrier, as is the practice in some ICUs, the dead volume would store 2.4 mg of phenylephrine regardless of the infusion rate ($Q_c = 0$). These drug masses would be potentially available as boluses should the carrier flow rate abruptly and dramatically increase or if a flush of crystalloid or other drug is given upstream through the infusion tubing. In general, the mass of drug stored in the dead volume increases with drug infusion dose rate, the stock concentration of drug (Fig. 1B), and the size of the dead volume (Fig. 1C).

The impact of an alternative possibility, the abrupt cessation of a carrier flow, on drug delivery was also
investigated. The total flow of fluid reaching the patient’s vasculature is the sum of the carrier and infused drug flows. As carrier flow abruptly ceases, fluid enters the patient only at the rate of the flow of infused drug. However, the concentration of drug will initially be small, reflecting the earlier dilution of drug by the carrier fluid. Consequently, the patient will initially receive a reduced drug dose for some time. For example, as predicted for phenylephrine (Cd = 1.2 mg/mL; I = 200 μg/min; Qc = 10 mL/h) the steady-state concentration of drug at the most downstream end of the infusion set will be 0.4 mg/mL. When the carrier abruptly ceases the total flow rate decreases from 15 to 5 mL/h, resulting in an initial drug infusion rate of 30 μg/min (Fig. 2). The slower the carrier flow before cessation, the closer the initial resulting infusion remains to the desired dose. At rapid planned drug infusion rates, the impact of suddenly stopping the carrier is diminished. In both of these instances, the drug infusion rate (Qd) is rapid relative to the carrier rate (Qc), and therefore, the initial dilution from the carrier is minimized. However, with rapid carrier flow before cessation, there is an initial large reduction in drug delivery. Note that these effects are independent of the dead volume (Eq. 4) but depend on the relative rates of drug and initial carrier flow.

In the event that the carrier flow is not restored and drug infusion continues, both the plug-flow and well-mixed models predict that the planned dose of drug will eventually be delivered, albeit with different kinetics (Fig. 3). The plug-flow model predicts an abrupt restoration to steady-state in one time constant, whereas the well-mixed model predicts a gradual return to steady-state over approximately three time constants. Both models have been previously described and experimentally validated (15).

Figure 2. Drug delivery rate immediately after carrier flow cessation, as a function of planned phenylephrine dose for initial carrier flow rates of 0, 10, 100, and 500 mL/h (Cd = 1.2 mL/h). The drug delivery is temporarily reduced when a carrier stops. The drug delivery rate is less than planned because dilute drug in the dead volume suddenly flows at a slower rate. The more rapid the initial carrier flow, the larger this reduction in drug delivery.

Figure 3. An example of the drug delivery after cessation of the carrier at zero minutes as described by the plug-flow and well-mixed models (V = 2 mL; Cd = 1.2 mg/mL; I = 200 μg/min). Drug delivery is initially reduced and returns to steady-state with kinetics that depend on the model. Whereas the plug-flow model shows a 50% reduction in delivered phenylephrine until the dead volume is completely turned over in one time constant, the well-mixed model predicts the same initial reduction, but a gradual return to steady-state over approximately three time constants. Both models have been previously described and experimentally validated (15).

Figure 4. Time to achieve steady-state after carrier cessation as a function of the dead volume, based on the plug-flow (lower bound, solid) and well-mixed (upper bound, dashed) models for planned phenylephrine doses of 40, 150, and 500 μg/min (Cd = 1.2 mg/mL). Note that the plug-flow model predicts a return to steady-state in one time constant (lower bound, solid), and the well-mixed model predicts a return to steady-state in approximately three time constants (upper bound, dashed). The actual time to steady-state must lie between the boundaries predicted by the two models, within the shaded regions. An example of the kinetics by which drug delivery returns to steady-state is shown in Figure 3.
well-mixed model predicts a gradual return to steady-state in approximately three time constants or 48 min. Should the absence of carrier flow be recognized and then become abruptly restored, the dead volume will contain stock drug, which may enter the patient as an undesired and potentially delayed bolus (15). The magnitude of the bolus will depend on the rate of infused drug flow, the size of the dead volume, the stock drug concentration, and the time elapsed without carrier flow.

The plug-flow model predicts the minimum time (one time constant) for achieving steady-state after changing either the drug infusion dose or the carrier rate (Equation 5; Fig. 5). This transition period is the time for a change in drug dilution by the carrier to propagate through the infusion system dead volume. The minimum delay will increase along with the size of the dead volume (Fig. 5A) and with the concentration of the drug in the stock solution (Fig. 5B). The delay decreases with carrier flow rate. The well-mixed model predicts a threefold longer time to achieve steady-state. The actual time to return to steady-state is between the boundaries defined by the plug-flow and well-mixed models (15).

**Discussion**

The use of continuous medication infusions is common in the clinical environments of the OR and the ICU. This is because many medications used in these environments, such as epinephrine or nitroglycerin, have short half-lives in the circulation. Sustained therapeutic effects can only be achieved with continuous infusion. In settings where the clinical condition of a patient may fluctuate rapidly, as during surgery or even in an ICU environment, there is a significant advantage to using medications whose effects are readily titratable.

Under- or over-dosing of powerful medications can have significant consequences. A bolus dose of phenylephrine or norepinephrine, if untreated, would probably result in significant vasoconstriction and hypotension lasting for at least a few minutes. Whereas some patients may tolerate this fluctuation in hemodynamics, those with failing ventricles, aneurysms, or tenuous tissue blood flow would be at risk for catastrophic complications. Conversely, a bolus dose of nitroglycerin or nitroprusside would, if untreated, probably result in significant hypotension lasting for at least a few minutes. Some patients with certain clinical conditions, such as aortic stenosis or vasocclusive disease of the cerebral or coronary circulations, might suffer sustained morbidity. The modeling demonstrated in this study, and validated in our previous study (15), predicts that such boluses of vasodilators and vasoconstrictors can occur under clinical conditions.

The potential for unplanned bolus delivery may be unrecognized because the magnitude of dead-volume reservoirs is unappreciated. IV infusion systems and various intravascular catheters may have significant dead volumes, ranging up to several milliliters (Table 1). As a rule of thumb, the maximum drug mass stored in the dead volume equals the dead volume multiplied by the stock-drug concentration (Equation 3 with $Q_c$ set to zero). If, for example, an infusion of phenylephrine or any other drug is mainlined into the side port of a pulmonary artery catheter introducer sheath, with a dead-space volume of 2.75 mL, a potential drug reservoir of hundreds to thousands of micrograms is established. This may be a safe and effective practice in the circumstance where one caregiver, such as an anesthesiologist or ICU nurse, is the
sole provider. However, in situations where multiple caregivers are involved, or when there is hand over of a patient from one team to another (for example, OR anesthesia team to ICU team or vice versa), the potential for error and harm is significant.

The predictions illustrated in this study concerning the time course of the return to steady-state after a perturbation in carrier or infusion dose rate are based on previously derived and validated computational models of IV delivery (15). An essential variable of the plug-flow model is the time constant, $\tau$, defined as the ratio of dead volume over total flow (Equation 5). This model fails to account for diffusion or dispersion of drugs within the infusion line, which may be significant at extremes of carrier flow. The well-mixed model better accounts for drug dispersion (15), and after any perturbation, predicts a gradual return to steady-state over three time constants. In reality, drug infusions likely behave between the extremes defined by these two models. This would effect only the absolute magnitudes of under- or over-dosing and the absolute duration of delays in drug delivery.

All of the predictions have been illustrated with phenylephrine; however, the equations are generic and can be applied to any drug given by IV infusion. The results of this study assume a fixed carrier flow rate. In reality, carriers are often gravity-driven so that flow will vary according to the height of the carrier fluid reservoir above the patient’s central venous pressure and with outflow resistance produced by a poorly running IV line. This adds a level of complexity to estimating the absolute concentrations of drugs in infusion tubing and the potential size of boluses. Also, with gravity-driven carriers, there may not be a true steady-state. With placement of a BP cuff proximal to the cannulation site, the flow rates become even more unpredictable.

To minimize safety problems, clinical personnel must first recognize the complexities of drug delivery by IV infusion. When transitions of care occur between providers, explicit descriptions of the architecture of infusion systems must be thoroughly communicated. However, practical steps to reduce the likelihood of drug errors would include (a) minimizing dead volume when constructing infusion setups, (b) ensuring a fixed rate of carrier flow, (c) using pumps with minimal fluctuations in output, and (d) mechanically preventing the possibility of upstream pushes of fluid, as by removing or blocking upstream side ports or stopcocks. Reducing the stock concentrations of infused drugs would build in safety, but this comes at the price of obligate additional fluid delivery to the patient.

Medication error accounts for a significant portion of preventable patient morbidity (16). Our findings are consistent with a role for infusion errors in patient morbidity attributable to methods of medication administration. The concepts presented in this study, whereas perhaps intuitive, may not receive full appreciation by novice caregivers, when multiple caregivers are involved, or when the clinical situation becomes particularly dynamic, such as during a resuscitation event. The models allow quantitative estimates of the magnitudes of dose alterations and delays in drug delivery. Recognition may ultimately have a patient safety benefit.

### Appendix

The drug delivery to the patient after the carrier flow ceases is predicted by the well-mixed model to be:

| Table 1. Approximate Dead Volumes of Some Commercially Available Catheters |
|-----------------------------|---------------------|------------------|
| Catheter | Port/lumen | Dead volume (mL) |
| Arrow 9.0F introducer via side arm | 3.2 |
| Arrow 9.0F introducer via side arm; PA line in place | 2.75 |
| Baxter/Edwards 8F AV Paceport PA CVP | 0.7 |
| | RA | 1.0 |
| | RV | 1.1 |
| Arrow single lumen 7F $\times$ 20 cm Proximal | 0.4 |
| Arrow double lumen $\times$ 20 cm Distal | 0.2 |
| Baxter/Edwards Vantax triple lumen $\times$ 16 cm Proximal | 0.47 |
| | Middle | 0.45 |
| | Distal | 0.56 |
| Baxter/Edwards quad lumen $\times$ 16 cm 18-gauge proximal | 0.31 |
| | 14-gauge medial 1 | 0.30 |
| | 18-gauge medial 2 | 0.29 |
| | 18-gauge distal | 0.65 |
| Abbott Lifeshield extension set | 4.0 |

PA = pulmonary artery; CVP = central venous pressure; RA = right atrium; RV = right ventricle.
Drug delivery w/ carrier off

\[ I(1 - e^{-t/\tau}) + \frac{I^2}{I + C_0Q_c} e^{-t/\tau} \quad (6) \]

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References

14. Lowenstein EA. A journey of the heart: cardiac anesthesia. In: Kitz RJ, ed. This is no humbug! Boston: Department of Anesthesia and Critical Care, Massachusetts General Hospital, 2002:319–21.