ABSTRACT
Chemically induced phlebitis continues to be an adverse reaction from the intravenous administration of infusates. The primary method used for decreasing the incidence of chemically induced phlebitis is to dilute infusates to the point where they do not cause tissue damage. The exact amount of dilution required for preventing chemically induced phlebitis is not currently known. This article describes methods for accurately determining the onset of chemically induced phlebitis and for describing the final concentration levels of infusates. Use of the tools presented could help intravenous therapy specialists refine research and, as a result, predict and possibly avoid chemically induced phlebitis.

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In the early 16th century, the physician Paracelsus wrote, “All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.” Dilution of toxicants (or poisons) is a principal method used to minimize damage caused by toxicants. Based on these statements, intravenous medicinal chemicals are toxicants whose adverse reactions are decreased by dilution.

An important adverse effect of intravenous therapy is the damage caused by the direct contact of infused chemicals with the inner lining of blood vessels. The degree of toxic insult to the healthy tissue is determined by the concentration of a toxicant in contact with the cells lining the inside of the vessel and by the duration of that exposure. This damage occurs primarily to the cells of the inner lumen of veins near the tip of intravenous catheters. This location is where the medication tends to be the most concentrated as it enters the body. Toxic damage to the cells of the inner lumen of veins can lead to inflammation of the vein (chemically induced phlebitis) and clot formation within the vein. Toxic insult to the vessels can lead to permanent vessel damage or more serious conditions such as infections of surrounding tissues or the bloodstream.

Dilution of a toxicant reduces the number of times that individual particles of that toxicant will make contact with susceptible tissue cells. Dilution essentially reduces the dose of toxicant that the average cell will receive. Dilution further reduces damage from toxicants by rinsing toxic particles off tissue cells, thereby minimizing the amount of tissue contact time.

Determining how much dilution is required to minimize the effects of toxicants can be logistically and intellectually challenging. Difficulties in determining risk include the high cost of testing, the legal complexities of research on laboratory animals as well as in humans, and the difficulties in measuring the toxicant activity in biological systems. Further complicating the predictability of adverse drug reactions at the blood vessel level are variations in individual responses to toxicants. Some individuals have mechanisms that counteract the delivery of toxicants and reverse the toxic injury. As a result, toxicity is not an inevitable consequence of exposure to toxicants because it may be prevented, reversed, or compensated for by such mechanisms. These difficulties help to explain why less than 5% of the 100 000 different chemicals released into the environment each year have reliable toxicity data. As a result of these and other reasons, the exact amount of dilution necessary to prevent chemically induced phlebitis secondary to the administration of any infusate is not known.
Scientific theory predicts that dilution of intravenous medications by any one or any combination of 3 methods of dilution will decrease the incidence of chemically induced phlebitis. These 3 methods for diluting intravenous medications are (1) increasing the amount of diluting solution in the administration container (while the amount of medication remains unchanged) prior to administration, (2) slowing the rate of administration of the medication into the blood vessel, and (3) infusing the medication into a vein with a larger volume of blood flow.

Dilution by mixing added extra diluent to an administration bag is straightforward and easy to quantify. However, dilution by blood, either by slowing the rate of infusion or by infusing the medication into veins with larger blood flow, is more difficult to quantify and therefore more difficult to predict. Variables pertaining to dilution by blood flow include not only the blood flow rate but also the position of the catheter tip in relationship to the walls of veins and the diameter of the catheter device compared with the diameter of the cannulated veins.

The diameter of the catheter compared with the diameter of the vein is a critical variable since the smaller the catheter, the greater the hemodilution. The reason is that the larger the catheter diameter is relative to the vessel lumen diameter, the less blood there is to flow unimpeded past the tip of that catheter. The second catheter-related variable has to do with the position of the catheter tip in relation to the inner walls of the blood vessel. The dilution effect of the blood is greatest when the catheter lumen tip is located in the exact center of the vessel lumen (Figure 1A). The closer the catheter tip is to a vessel wall, the less blood will dilute the infused medication before it contacts the vessel wall (Figure 1B). The extreme case of this variable occurs when a catheter tip is positioned perpendicular to and is against a vessel wall or other vascular structure (Figure 1C). In that case, there is essentially no dilution effect from the blood—the toxicant is no more diluted when it strikes the vessel wall than it is in the initial administration container. The concept of proximity of the toxic discharge in relationship to the vein wall is similar to the principles used to minimize the toxic effects of pollutants discharged into rivers.

**PREDICTING INTRAVASCULAR TOXICITY**

A primary goal of toxicology is to predict the minimum concentration (or dilution) of individual toxicants that will cause adverse reactions. As a result of this information, these toxicants can then be diluted to or below those identified concentrations so that adverse effects will not occur. Similarly, a goal of intravenous therapy should be to predict the minimum dilution necessary for every infusate that would ensure the absence of chemically induced phlebitis.

There are only a few crude methods currently available that attempt to predict and prevent chemically induced phlebitis. Drug manufacturers and pharmaceutical texts provide some general guidelines for administration of chemicals that are particularly known to cause phlebitis. For example, in the case of vancomycin hydrochloride, the manufacturer maintains that phlebitis may be minimized by using dilute solutions and rotating injection sites. The Infusion Nurses Society recommends that those infusates with pH less than 5 (such as vancomycin) or greater than 9 and intravenous therapies with osmolality greater than 600 mOsm/L will cause chemically induced phlebitis when infused peripherally and, as a result, must be administered directly into the superior vena cava. Unfortunately, these guidelines will not prevent all cases of chemically induced phlebitis. For example, the aforementioned
Infusion Nurses Society guideline does not address the fact that chemicals cause phlebitis for reasons other than extremes in osmolality or pH.23 Even with the use of the previously noted tools, chemically induced phlebitis is not prevented consistently. All short peripheral intravenous catheter sites are recommended to be rotated on a regular basis precisely because phlebitis is an expected outcome.24,25

The science of toxicology has a useful tool for predicting toxic responses that ought to be adapted to intravenous therapy. Toxicology uses an outcomes research-based tool that establishes the safe concentrations of individual chemicals. Toxicologists refer to this safe concentration level as the “no observed adverse effect level” or NOAEL.8 In intravenous therapy, as it regards the incidence of chemically induced phlebitis, the safe concentration would be synonymous with the safe dilution level. Any concentration or dilution level of an infusate that does not cause adverse effects (as evidenced by outcomes research) can be said to be within the NOAEL. Insufficiently diluted infusates that result in chemically induced phlebitis can be said to exceed the NOAEL.

Several reasons why the NOAEL for any toxicant is difficult to determine have already been discussed in the introductory paragraphs of this article. However, there are 3 particular reasons why it has been difficult to identify the NOAEL for intravenous therapies. First, in outcomes research, initial evidence of the adverse effect of phlebitis is difficult to identify consistently. Second, chemically induced phlebitis closely mimics phlebitis caused by other factors. Third, the many variables essential to determining final dilution levels have been inadequately represented in intravenous therapy outcomes research.

When the NOAEL related to chemically induced phlebitis is exceeded in intravenous therapy, the initial toxic response is hidden from view and, as a result, researchers cannot record the onset of those adverse effects. Only when the damage has advanced enough to spread to surrounding tissues (as evidenced by edema, redness, pain, and induration) do researchers see and record the onset of phlebitis.26-32

Even when the damage spreads to surrounding tissues, there is certain to be variation in reporting of adverse effects as the cannulated veins are of varying depths. This variation in reporting occurs because phlebitis is simply more readily observed in shallow veins than in deeper veins. A solution to this research problem would be regularly scheduled ultrasonography examinations to identify clearly early signs of chemically induced phlebitis, which include thickened vein walls and early thrombus formations distal to intravenous catheter tips.

In outcomes research, the signs and symptoms of chemically induced phlebitis have been difficult to distinguish from those of mechanical (catheter-induced) phlebitis, organism-induced phlebitis, or genetic predispositions for phlebitis.26,33 To help identify NOAELs, future outcomes research should include detailed and regularly scheduled ultrasound examinations of the entire vein segments where there is a catheter present. Identification of clots in the segment of the vein along the body of the catheter as opposed to clots found initially only in the vein segment distal to the tip could help to distinguish mechanically induced phlebitis from chemically induced phlebitis. Clots formed along the body of the catheter are more likely to be mechanically induced, while clots at or near the catheter tip are more likely to be caused by the infused medication. An exception to this rule may be when the catheter tip is rubbing against a vein wall, which could theoretically lead to mechanical phlebitis. In those cases, ultrasound examination could identify when catheters are butted into vein structures and result in elimination of those catheters from chemically induced phlebitis outcomes research. Blood culture or catheter tip cultures could help to distinguish organism-induced phlebitis from chemically induced phlebitis. Blood tests can help to determine the presence of genetic tendencies for phlebitis in research participants. Only when the other possible reasons for phlebitis have been ruled out through research can NOAELs for chemically induced phlebitis be determined.

Much of the research conducted on the adverse effects of intravenous therapy on veins has insufficient information pertaining to dilution factors.31,34,42 Variables that must be accounted for in chemically induced phlebitis outcomes research include the names of medications administered through the catheters, initial dilution in the administration containers, dose administration frequency, number of days of therapy, duration of each infusion, catheter tip position relative to vessel walls, catheter diameter compared with vein diameter, and average blood flow at the internal catheter tip. It should be noted that the variables of catheter tip position, catheter diameter compared with vein diameter, and blood flow rates at the catheter tip were not even possible to ascertain until the advent of ultrasonography. Since all of these dilution variables affect the number of hits and length of exposure of infused toxicants to susceptible vein tissues, they must be fully described if the research results are to be used for determining NOAELs of specific therapies.

MEASURING INTRAVENOUS THERAPY DILUTION VARIABLES

The determination and acceptance of universally recognized NOAELs in intravenous therapy will require consistent measurement of final dilution of infusates. Determination of the final dilution measurement requires specific calculations and equipment.
Diluting a chemical in a container prior to administration is the most commonly used method of dilution and is the easiest to quantify. For example, a gram of a particular medication comes in a 20-mL bottle supplied by the manufacturer. The medication is already diluted into a solution of approximately 50 mg/mL. The concentration of the medication can easily be diluted to, for example, 4 mg/mL by simply adding 200 mL of diluent to the initial solution.

The second method of dilution used in intravenous therapy is to increase the length of time over which a chemical is administered. This results in increased mixing with a larger but unmeasured volume of blood. For example, the previously mentioned 4 mg/mL concentration may be administered over 90 minutes instead of 30 minutes. In this case, the medication is hypothesized to be diluted by 3 times more intravenous blood volume than when administered over 30 minutes. The actual volume of blood used in this method of dilution is currently not measured in intravenous therapy.

The third method of dilution relies on the assumption that blood flow volumes increase the closer to the heart that the infusion occurs. This method involves advancing catheter tips into veins with ever-larger blood flow volumes. The result is dilution from the same principle as slowing the rate of infusion; that is, there is less medication infused per volume of blood (the diluent). The actual volume of blood used in this method of dilution is also currently not measured in intravenous therapy.

There is little evidence that average blood volume flow rates in peripheral veins have been the subject of research or otherwise quantified. It has been suggested that there is a lack of research regarding veins of the upper extremities because until recently there was little need for this information.

Knowing the blood volumes and flow rates where infusates enter the vascular system is essential in determining the final degree of medication dilution. Individual vascular flow rates will vary depending on patient vascular anomalies, physical activity, age differences, patient size, health conditions, and normal variations in vascular structures. As a result, individual vascular blood flow rates will probably differ from any predetermined average flow rate. The most accurate dilution computations then will be based on measurement of each patient’s real-time blood flows. For purposes of presenting the formula in this article, a rough estimate of flow rates of certain veins has been determined on the basis of the known (resting) cardiac output of 5000 mL/min in an average adult (Appendix). These estimates serve as a foundation only for calculating final dilution in the examples in this article.

Advanced ultrasound technology can be used to measure the actual blood flow rates in veins commonly used for intravenous therapies. Ultrasound is used to obtain a Doppler sample of vascular blood flow speed in meters per second. That blood flow speed is then multiplied by a measurement of the area of the vein lumen at the same location the Doppler sample is taken. This calculation then gives the blood flow rate or, in other words, the actual volume of blood per unit time flowing at a specific location.

### MEASURING FINAL DILUTION

Risk assessments for specific toxicants must include a description of how much toxicant reaches susceptible tissues. The authors of this article developed the following formula to quantify the concentration of any intravenous chemical at the point of entry into veins. This formula should help to determine the NOAEL related to the adverse effect of chemically induced phlebitis for intravenous medications.

The proposed dilution equation is as follows:

\[
\text{Drug amount (mg)} \times \frac{\text{Pump flow rate (mL/min)}}{\text{Initial dilution (mL)}} \times \frac{\text{Vein flow rate (mL/min)}}{\text{Final dilution (mg/mL)}}
\]

The following example demonstrates how to determine a typical final dilution with a hypothetical antibiotic “Z”:

\[
\frac{1000 \text{ mg antibiotic “Z”}}{100 \text{ mL} \text{ 0.9% NaCl}} \times \frac{100 \text{ mL/60 min} = 1.7 \text{ mL/min}}{135 \text{ mL/min (cephalic vein) blood}} = 0.13 \text{ mg/mL}
\]

Imagine that future outcomes research finds the NOAEL for chemically induced phlebitis with use of antibiotic “Z” is 0.1 mg/mL or less. It is apparent then that 1 or more of the variables in the aforementioned equation needs to be adjusted to decrease the final concentration of the antibiotic.

This second example demonstrates how simply locating a new catheter in a blood vessel with a greater flow rate results in a final dilution that is well within the known NOAEL of 0.1 mg/mL or less for antibiotic “Z”:

\[
\frac{1000 \text{ mg antibiotic “Z”}}{100 \text{ mL/60 min} = 1.7 \text{ mL/min}} \times \frac{270 \text{ mL/min (axillary vein) blood}}{100 \text{ mL} \text{ 0.9% NaCl}} = 0.06 \text{ mg/mL}
\]

Now imagine that a long-arm catheter is contraindicated and that a short peripheral catheter in the distal cephalic vein above the wrist is the patient’s only access. Assume that an ultrasound examination of that vein near the catheter tip reveals an actual flow rate of 90 mL/min. In this case, note how the initial container
concentration and the pump flow rate can be adjusted in the formula to ensure that the antibiotic “Z” NOAEL of 0.1 mg/mL can still be met:

\[
\frac{1000 \text{ mg antibiotic “Z”}}{120 \text{ mL 0.9% NaCl}} = \frac{100 \text{ mL/100 min}}{90 \text{ mL/min (distal cephalic) blood}} = 0.09 \text{ mg/mL.}
\]

As this formula demonstrates, any of the 3 dilution factors in the equation (pump rate, catheter tip position, or initial container dilution) may be adjusted for any patient’s particular needs to determine and ensure the final dilution/concentration of a medication.

**DISCUSSION**

Intravenous therapy needs an effective tool that prevents chemically induced phlebitis. When patients incur permanent damage to their vein secondary to phlebitis, their future vascular access options are reduced or eliminated. Currently our tools are often contradictory and/or based on relatively weak science. For example, some health care professionals insist that certain drugs (such as vancomycin) must be diluted by the blood flow within the superior vena cava while some researchers demonstrate that these same drugs can be safely infused via peripheral veins. Some research has shown that neither a higher initial dilution nor slowing the infusion resulted in decreased incidence of phlebitis. It is not surprising that research outcome data, professional opinions, and actual practices pertaining to dilution theory vary widely when all of the factors affecting final dilution are inconsistently controlled.

There is no reasonable single method for preventing chemically induced phlebitis. It has been suggested that simply infusing all medications into the central vascular circulation is a cheap and relatively safe method for diluting medications. This suggestion is unsound in light of the life-threatening issues inherent with centrally placed intravenous catheters that do not exist with more peripherally located catheter tip positions. Other problems specific to central catheter placements include the need for specialized equipment to place the catheters centrally, the need for radiography to confirm proper tip positions, a complex sterile insertion procedure, and increased insertion costs. Furthermore, there is no evidence that simply infusing medication into central vascular blood flow ensures that the medications are diluted to their NOAEL. Conversely, an argument could be made that diluting all medications to their respective NOAEL in their initial containers would be the safest and easiest method of dilution. However, diluting all medications in their initial containers to the NOAEL dilution level has some serious drawbacks as well, such as patient fluid overload. Even dilution by simply extending infusion times may interfere with the therapy mechanism of action as is the case with many antibiotics and total parenteral nutrition. It is clear then that providing sufficient dilution to avoid chemically induced phlebitis requires a more sophisticated and individualized approach.

With the aid of advanced ultrasound technology and calculations similar to the aforementioned formula, it should be possible to identify the NOAEL for each infused chemical and to prevent chemically induced phlebitis. Infusion nurse specialists are uniquely suited for using these tools in light of their experience with intravenous therapies and their basic understanding of ultrasonography. In the future, infusion nurses’ most important role should be performing initial vascular ultrasound assessments to determine the blood flow rates in pertinent veins for patients requiring complex intravenous therapy. The infusion nurse can then develop intravenous therapy care plans for each patient based in large part on those assessments. These customized plans would logically include recommendations for insertion sites, optimal final catheter tip positions, and in collaboration with pharmacists and physicians, suggestions for other aspects of dilution such as pump flow rates and initial container dilution. The role of the infusion nurse should further be expanded to include performing regularly scheduled ultrasound examinations of the cannulated veins during therapy courses to identify the earliest signs of phlebitis. It follows that infusion nurses should participate in outcomes data collection and research so that NOAELs are continuously identified and refined.

With these advancements in the application of dilution theory, infusion therapies could truly be considered remedies instead of poisons, as chemically induced phlebitis becomes a phenomenon of the past.

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**REFERENCES**


Appendix

For purposes of this article and in light of the lack of published data otherwise, the method used to estimate average vascular flow rates in the superior vena cava, innominate, subclavian, and axillary veins (of an adult at rest) is as follows:

1. The cardiac output (in an average adult at rest) is 5000 mL/min.
2. The cardiac input (in the right atrium) is equal to cardiac output at 5000 mL/min.
3. The blood flow in the superior vena cava is 2500 mL/min (ie, one-half of the cardiac input with the remaining half supplied by the inferior vena cava).
4. The blood flow in each innominate vein is approximately 1200 mL (the flow of the superior vena cava divided by 2).
5. The blood flow in the innominate veins is provided predominantly by the subclavian and both jugular veins, assuming that equal blood flow contribution means that both jugular veins and the subclavian have flows of an estimated 400 mL/min.

6. The blood flow in each subclavian vein comes from the cephalic and axillary vein. The axillary vein flow comes from the basilic and brachial veins. The flow of each of the basilic, brachial, and cephalic veins is approximately one-third of the 400 mL of the subclavian or about 135 mL/min. The axillary flow would be the combined flow of the basilic and brachial, or about 270 mL/min.

Erratum

Intraosseous Route as Alternative Access for Infusion Therapy: Erratum

In the May/June 2010 issue of the Journal, a misspelling appeared in reference number 27 on page 174 in the article “Intraosseous Route as Alternative Access for Infusion Therapy.” The interviewee’s last name is Rolt, not Holt. This error has been noted in the online version of the article, which is available at www.journalofinfusionnursing.com.

Reference: