Radiopharmaceuticals

Two Methods of Preparation of Xenon-133 Saline Solution

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Two procedures for dissolving ^{133}Xe gas in isotonic saline simply and economically with reasonably high activity concentrations are described. The first method is a modification of a previously described procedure and introduces a new flow-through mixing system allowing for a more homogeneous preparation. This system can be used with significant cost and time savings in a department with large clinical demand (> 3 patients per week). The second method is a system which can be used economically in a department with a small and/or sporadic clinical demand. This technique involves the preparation of single-patient dose by introducing saline into commercially available ^{133}Xe gas vials. The solubility of ^{133}Xe in saline can be significantly increased (> 50%) by introducing saline into a ^{133}Xe gas vial and incubating the reactive vial at 4 °C for 3 hr or more. The suggested modifications are simple and the resultant activity concentrations are relatively high and clinically useful.

The measurement of cerebral blood flow (CBF) and the assessment of tissue perfusion in extremities by the analysis of ^{133}Xe saline clearance technique has been described (1–4). At this time, however, preparations of ^{133}Xe gas dissolved in isotonic saline are not commercially available. CBF studies in our laboratory require an activity concentration of at least 15 mCi dissolved in no more than 5 cc of saline (3 mCi/cc) to produce adequate count rates and meaningful clinical results. Other investigators (5,6) have described a variety of procedures for dissolving ^{133}Xe in isotonic saline with efficiencies ranging from 10%–30%. We set out to develop a practical procedure which would be technically simple and yet yield a high solubility of ^{133}Xe gas in isotonic saline.

Two general approaches to the problem of dissolving xenon gas into saline were investigated. The first method involves the dissolving of a large quantity of ^{133}Xe gas (1–1.5 Ci) into ~ 10 cc of saline in order to have a continuous supply of ^{133}Xe saline solution over a two-week period. The second method involves the preparation of a relatively small quantity of ^{133}Xe saline from a commercially available ^{133}Xe gas vial* containing from 20–40 mCi of ^{133}Xe on the day of delivery. This paper

discusses some of the problems encountered with these two procedures and presents the techniques used to optimize these methods for a variable patient load.

MATERIALS AND METHODS

Method 1

This method represents a modification of the procedure first described by Carroll et al. (5). A 5-in. long quartz glass ampule containing a dispensing neck and 1 Ci of ^{133}Xe gas in a closed equilibration chamber separated by a conical glass seal (Fig. 1) was commercially obtained on a periodic basis. Upon receipt of a shipment, the xenon ampule was immediately taken out of the shielding cylinder, and the radioactivity was measured in a dose calibrator. The ampule was then placed in a lead holder, and sterile saline was aseptically introduced into the dispensing neck. A sterile, gray 13-mm Teflon septum was placed on top of the saline-filled dispensing neck and sealed with an aluminum crimp. A saline-filled sterile spinal tap needle and a 19-gauge needle were then placed through the septum. These needles were attached to a saline-filled flow-through system that we designed (Fig. 2). Once this system was tested and no air leaks were found, the spinal needle was then advanced to puncture the inner glass seal of the equilibration chamber. The vacuum inside the ampule equilibration
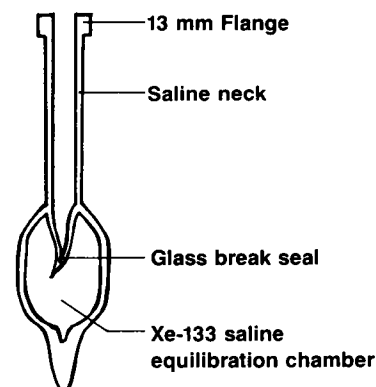
FIG. 1. Glass equilibration ampule containing 1–1.5 Ci of ^{133}Xe.

Labels: 13 mm Flange; Saline neck; Glass break seal; Xe-133 saline equilibration chamber
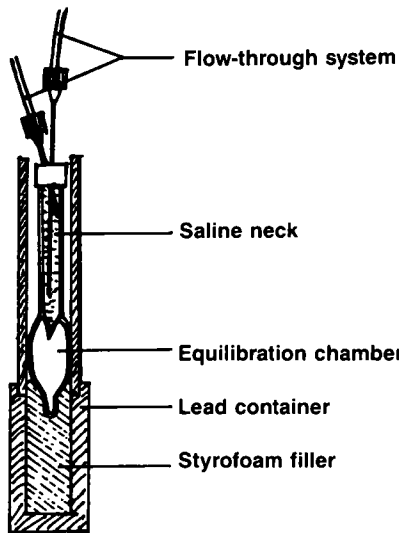
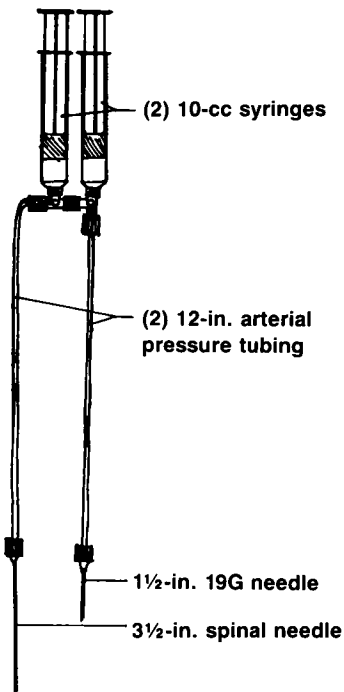FIG. 2. Flow-through system for use with xenon ampule.

FIG. 3. The spinal needle of the flow-through system is shown in position just before it is pushed through the glass seal into the equilibration chamber. Note that saline should be passed from the flow-through system into the saline neck area to assure that there are no leaks or gas bubbles present before the glass seal is broken.

chamber drew in ~ 7 cc of sterile isotonic saline from a syringe attached to the spinal needle (Fig. 3). The short-loop double syringe system that was initially described and used by Carroll et al. (5) was difficult to handle and frequently leaked. We also found that we could not conveniently predict or control the activity concentration. Consequently, we designed a lower pressure system that was less likely to leak, used more saline volume, and yielded a more predictable and homogeneous activity concentration. In order to obtain a homogeneous activity concentration, the new flow-through
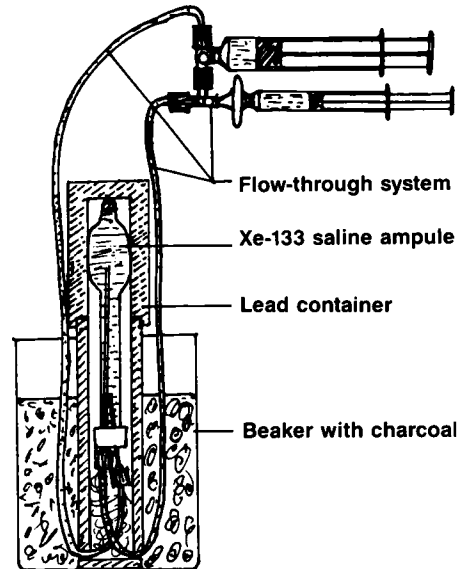

FIG. 4. Assembled xenon in saline dispensing system as described in Method 1.

system, which was connected to the equilibrium chamber, was flushed several times as demonstrated in Figure 4. Special attention should be paid when attaching the flow-through system so that no air bubbles are introduced as fluid is passed from one chamber to the other. The system was flushed by passing a precalculated volume of saline (usually 3–5 cc) from one syringe through the equilibrium chamber to the other syringe several times.

It has been our experience that the original injected saline volume was usually smaller than the void volume of the xenon equilibration chamber so that a small gas bubble ~ 3–4 mm in diameter remained in the equilibration chamber. Radioxenon rises in an aqueous medium; consequently, our investigations and those of others have reported (3,7) that the glass ampule should be stored upside-down in a lead shield and maintained in that position while in use. The lead shield containing the ampule was also placed in a 500-cc plastic beaker filled with activated charcoal. The charcoal serves as a xenon trap and was used to check for ampule leaks. Although ^{133}Xe leaks cannot be accurately measured by this technique, their existence can be detected. After the ^{133}Xe saline has been used, the charcoal is placed in a well scintillation counter and assayed. At no time was the observed count rate > 10 times the background. Calculated decay curves and observed activity decay curves of the reaction vials were compared and no significant differences were found.

After the ^{133}Xe saline has been prepared and allowed to equilibrate at room temperature for at least 45 min, patient doses may be dispensed.

Method 2

This method represents a variation of the procedure of Herold et al. (6). An air-tight 3-cc glass vial of ^{133}Xe gas intended for xenon ventilation studies was used. These vials are prepared by the supplier to contain 20–40 mCi of ^{133}Xe gas on the day of delivery with carbon dioxide gas as a diluent. Upon
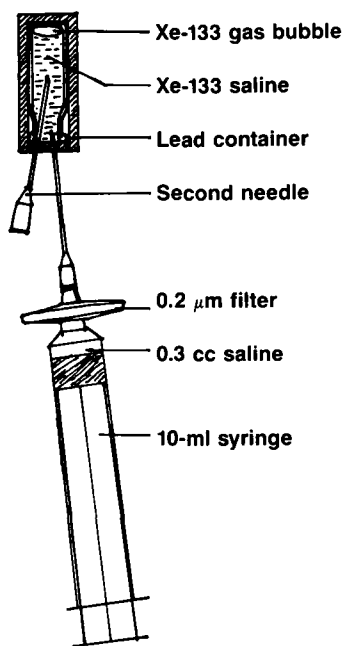
FIG. 5. Dispensing of 133Xe in saline as described in Method 2.

receipt of the vial, the radioactivity was measured in a dose calibrator. If the gas is transferred to another container or vial, attention must be paid to any changes in vessel attenuation and geometry. We found a dose attenuation factor which averaged 1.2 when the container type is changed during the study (i.e., glass ampule as opposed to plastic syringe).

After measuring the radioactivity, the xenon gas vial and a supply of sterile saline are cooled to 4 °C in a refrigerator for at least 15 min. Using a 5-cc syringe equipped with a 19-gauge needle, 3 ml of cold isotonic saline are withdrawn from the supply vial. Cold saline is then injected into a xenon gas vial and the volume of cold saline used (usually 2.8–2.9 cc) is noted. Saline should not be pressed or forced into the vial. There is a slight negative pressure in the xenon gas vial at the time of shipment so that saline is easily introduced into the container without force. As in Method 1, the injected volume is usually smaller than the void volume of the vial. Thus, a small gas bubble may remain above the saline. This bubble should be kept as small as possible throughout the study. Measure and record the activity of 133Xe saline in the vial. Store the vial at 4 °C in a refrigerator for at least 3 hr (or for longer periods of time if desired).

When dispensing the 133Xe saline dose, measure the activity of the xenon-saline vial and record the measurement. Prepare a 12-cc sterile glass syringe equipped with a 19-gauge, 1½-in. long needle attached to a 0.22-micron microfilter. Withdraw 0.3 cc of cold saline from the isotonic saline stock bottle into the prepared sterile syringe system. (This displaces any air in the microfilter.) Insert a second needle through the septum of the 133Xe saline vial until the tip of the needle reaches the middle of the vial. This second needle is open to the air and will allow air to enter the vial when the saline is withdrawn. Following completion of this step, the xenon-saline vial should be inverted and the sterile syringe system (described

above) inserted. Saline is withdrawn immediately (Fig. 5). Withdraw the syringe from the vial and replace the microfilter with a new needle that should be capped tightly and pointed downward. The dose is now ready for the patient study.

Measure the activity left in the xenon saline vial and calculate the theoretical dose in the syringe. Usually, small amounts of 133Xe (1–2 mCi) are lost in the transfer, and this amount can be estimated by subtracting the activity in the syringe from the activity in the vial after correcting for absorption. The amount of xenon dissolved in the isotonic saline can be calculated as follows:

$$\% \text{ dissolved} = \frac{\text{saline syringe activity}}{\text{initial gas vial activity} \times 1.2} \times 100$$

or

$$\frac{\text{initial gas activity} - \text{residual gas activity} \times 100}{\text{initial gas activity}}$$

RESULTS

Method 1

The average activity concentration (mCi/cc) of the saline obtained 45 min after preparation was 55.4 mCi/ml with a range of 42–61 mCi/ml of saline. The rate at which the activity concentration decreased over time was usage dependent. There was an accelerated decrease in the activity concentration over time with increased usage. An average of five doses over a two-week period was usually required to meet our clinical demands with reasonable cost per dose. However, as many as eight patient doses over a two-week period, with activity concentration > 5 mCi/ml, could be obtained. The equilibrium chamber was not subjected to low temperatures for practical and radiation safety reasons. Repeated measuring of activity in the 133Xe ampule revealed only a small loss of activity (50–150 mCi) because of flushing of the equilibrium chamber. Samples sent to the laboratory for pyrogen and sterility testing were negative.

Method 2

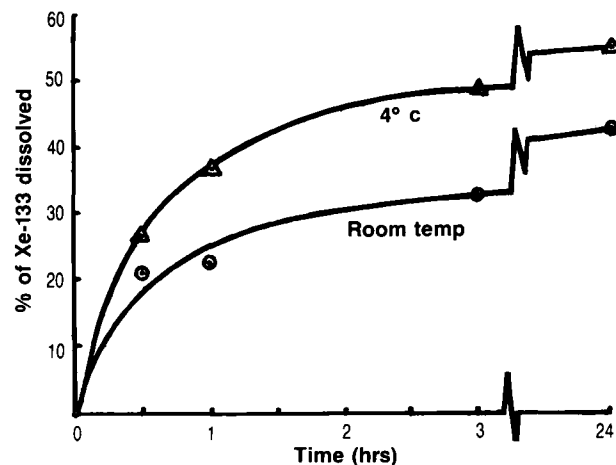Xenon activity concentration solubility was studied when

FIG. 6. Effect of temperature and incubation time on the percent solubility of 133Xe.

TABLE 1. Effect of Incubation Time and Temperature on Solubility (%) of Xenon-133

Temperature	Time (hrs)			
	0.5	1	3	24
Room temperature	20.8* ± 2.4	21.7 ± 2.2	32.7 ± 1.5	43.4 ± 3.6
4°C	25.7 ± 1.6	36.1 ± 1.4	47.9 ± 5.5	54.7 ± 3.5

*Number represents mean percent ^{133}Xe solubility and standard deviation.

temperature and incubation times were varied. Table 1 and Figure 6 demonstrate that lower temperatures (4 °C) and longer incubation periods (1-5 hr) significantly increase ^{133}Xe solubility in isotonic saline.

Xenon solubility in saline for 30 min at room temperature yielded an efficiency from 19%-24%. Dissolving xenon gas into saline and incubating for 30 min at 4°C increased the solubility from 23%-27.5%. Extending the incubation period at 4 °C continued to increase solubility up to a range between 40%-56%. Incubation beyond 5 hr did not significantly improve solubility (Fig. 4). As in Method 1, all samples were found to be sterile and pyrogen free. Repeated measuring in the dose calibrator revealed no loss of activity because of leakage.

DISCUSSION

Two procedures for dissolving ^{133}Xe gas in nondegassed isotonic saline under a constant atmospheric pressure have been described. Method 1 involves purchasing a large quantity of ^{133}Xe gas (1.0-1.5 Ci) in a disposable glass ampule with an equilibrium chamber. A dynamic equilibrium between a trapped bubble of ^{133}Xe gas and a small volume of periodically renewed saline is established and maintained in the equilibration chamber. This system yields ^{133}Xe saline doses with predictable and homogeneously high activity concentrations for intravenous administration when our extended flow-through system was used. This method is ideal and cost-effective for a nuclear medicine laboratory that has a continuous flow of patients for CBF, cardiac, tissue perfusion studies, and lung studies.

A saline flow-through system was constructed in our laboratory which was found to be convenient and essentially leak-proof (Fig. 4). This system allows for good mixing of the new and old saline and yields predictably high and homogeneous activity concentrations. The ability to maintain similar patient doses by altering saline volume in a predictable fashion is an important quality control factor in our clinical studies. Initial activity concentration (Day 1) averages 42-61 mCi/ml of solution and, if no doses were withdrawn, final activity concentrations between 8-10 mCi/ml on Day 14 were observed. The rate of decrease in activity concentration was usage dependent. As many as nine patient doses can be drawn from this system if the solution is withdrawn within five days after preparation. Five patient doses, with sufficient activity, can

be drawn from the system if they are drawn over a 14-day period on a random basis. All patient samples must have an activity concentration of > 3 mCi/ml of saline in order to meet the requirements of our CBF procedure. Cost per patient dose is quite prohibitive if five preparations per ^{133}Xe ampule are not used.

In Method 2, saline is injected into air-tight 3-cc commercial glass vials of ^{133}Xe gas under slight negative pressure. The average volume injected varied between 2.7-2.9 cc depending on the age of the vials. Commercial vials that are approaching their expiration date at the time of delivery contain less activity and acceptably less saline. We speculate that minute leaks must exist which allow small amounts of air to enter the ^{133}Xe vial, and thus decrease the amount of negative pressure and space available for saline introduction at the time of preparation.

The use of small commercially available xenon gas vials and sterile isotonic saline is inexpensive, easy to handle, and a relatively simple procedure to set up in a laboratory. It is economically attractive to those nuclear medicine laboratories that receive sporadic orders for studies. The dissolving procedure can be performed at room temperature with a solubility efficiency of around 20%. This solubility can be increased to 26% if the saline and xenon are pre-cooled to 4 °C (refrigerator) and incubated 30 min immediately after preparation. This observation agrees with the findings recently reported by Herold et al. (6). We were able to improve this solubility to 48% by incubating the xenon saline preparation for 3 hr at 4 °C. Best results were obtained with overnight incubation at 4 °C (Table 1).

Xenon-133 saline prepared from commercial gas ampules provided for ventilation studies is not presently an FDA-approved injectable radiopharmaceutical in the U.S. The steps for assuring sterile and pyrogen free saline samples, however, are relatively simple. A limulus test must be performed prior to patient administration. Those institutions without a broad license will have to obtain a special IND for use in their laboratories.

FOOTNOTE

*DuPont Diagnostic Imaging Div., North Billerica, MA.

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