Radiopharmacy

Preparation of Xenon-133 Solution for Intravenous Administration

Thomas J. Herold, Mrinal K. Dewanjee, and Heinz W. Wahner

Mayo Clinic and Mayo Foundation, Rochester, Minnesota

A method for routine preparation of a solution of ^{133}Xe gas in saline from commercially available ^{133}Xe gas ampoules is described and evaluated. At room temperature and atmospheric pressure, about 25% of the ^{133}Xe gas dissolves in saline. Xenon-133 binds to the syringe wall or may escape into the air when stored in sealed plastic syringes. Preparation immediately prior to use, short-term storage in a properly closed glass vial, and assay of the syringe for activity before and after injection are important considerations for delivering accurate amounts of ^{133}Xe gas in saline solution.

Preparations of Xenon-133 (^{133}Xe) gas dissolved in isotonic saline are not commercially available because of their infrequent use in most nuclear medicine laboratories. Some laboratories, however, may still occasionally have a use for ^{133}Xe in saline (e.g., monitoring the position of a central venous catheter in evaluation of a right-to-left cardiac shunt). After it is given intravenously, this inert gas is rapidly exhaled, and there is no recirculation or background problem when this tracer is given prior to another isotope. It can be used for measuring tissue perfusion by observing the rate of removal from a site of intracutaneous injection as a test for adequate arterial blood supply (*1,2*), for some cerebral blood flow studies with multiple-probe instruments (*3*), and for lung imaging. As a response to this recent shortage, DiPiazza and Harbert (*4*) described a simple procedure for dissolving ^{133}Xe gas in saline with an efficiency of about 10%.

The objectives of this study were: to evaluate whether this procedure could be made more efficient by maximizing the amount of ^{133}Xe dissolved in the solvent; and to develop a simple and cost-effective procedure for producing ^{133}Xe in saline for intravenous use in the setting of a general nuclear medicine radiopharmacy.

For reprints contact: Heinz W. Wahner, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

MATERIALS AND METHODS

Air-tight glass 3-ml vials of ^{133}Xe gas* were used as starting material. These sterile vials were prepared by the supplier to contain 20–50 mCi of ^{133}Xe on the day of delivery. Radioactivity was measured with a dose calibrator. Sensitivity of the instrument was calibrated according to the guidelines outlined by Suzuki et al. (*5*). At the dose range used in this study, the measurement of ^{133}Xe had a coefficient of variation of less than 2%. Because of high sensitivity to changes in source geometry and type of container (material and wall thickness) when ^{133}Xe is measured in an ionization chamber (*5*), all measurements were done on samples in identical glass ampoules or identical plastic syringes. (These differed by a factor of 1.2.) Plastic (polystyrene) syringes (3 ml) and stainless steel needles (25 gauge) were used for all studies. The procedures were conducted in a vented hood, and lead shielding was used to protect the operator.

Gas Solubility at Environmental Atmospheric Pressure and Changing Temperatures

Three-milliliter samples of sterile isotonic saline, 5% and 25% human serum albumin, 10% fat emulsion (Liposyn), or undiluted olive oil were introduced (with a 3-ml syringe and a 25-gauge needle) into the original glass vials containing the ^{133}Xe. Because the injected volume was smaller than the volume of the vial, a gas bubble about 2-mm in diameter remained above the solvent. The vial was incubated for 5 min and then the solvent was withdrawn with a syringe. Both the ampoule and the syringe were assayed for radioactivity. Some ^{133}Xe was lost in the transfer; this amount was estimated by subtracting the activity in the syringe from the activity in the vial after correction for absorption. The fact that there was ^{133}Xe escape during the transfer of the solvent from vial to syringe was also established by monitoring the hood with an airflow counter during the procedure.

The amount of ^{133}Xe dissolved in the solvent was calculated by:

$$\% \text{ dissolved} = \frac{\text{syringe activity (mCi)} \times 100}{\text{initial vial activity (mCi)} \times 1.2},$$

1.2 being the correction factor for the attenuation difference between the glass vial and the plastic syringe. The entire procedure was performed with the solvents at room temperature and at 4 °C at incubation times of 5, 20, and 30 min with ^{133}Xe vials of different ages (length of time after preparation by the company).

Storage of ^{133}Xe Gas in Saline

For this study, syringes containing ^{133}Xe in saline and sealed with a metal seal were stored in a hood and assayed repeatedly. The loss of radioactivity in excess of the decay was attributed to escape of ^{133}Xe. The syringe was emptied into a vial (that was discarded) and assayed again. The activity that could be removed from the syringe was calculated for the different time intervals of storage. The residual activity in the syringe was considered to be due to uptake by the plastic material.

Xenon-133 Gas Escape from Ampoules

Ampoules punctured for introducing and withdrawing the solvent were assayed repeatedly to measure loss of radioactivity.

RESULTS

Gas Solubility

Solution efficiency was dependent on temperature, solvent used, and, in some experiments, incubation time (Table 1). Isotonic saline was a better solvent than olive oil, Liposyn (10%), or human serum albumin at 5% or 25%. Olive oil and Liposyn were better solvents at 4 °C than at room temperature, but this was not observed for isotonic saline. The poorest solubility was found in human serum albumin, and so no further experiments were conducted with this solvent.

The duration of the incubation in saline affected the amount of ^{133}Xe dissolved (Fig. 1). The greatest amount of gas dissolved (mean, 35.7%) was obtained with isotonic saline at 4 °C with 30 min of incubation. However, this value had the largest standard deviation which was probably due in part to the difficulty of maintaining the temperature at 4 °C during the procedure. An increase in the amount dissolved with increasing incubation time was not noted when the experiments were performed at room temperature (25 °C). Thus, the maximal amount of ^{133}Xe gas trapped in isotonic saline at room temperature was about 25%, regardless of incubation time.

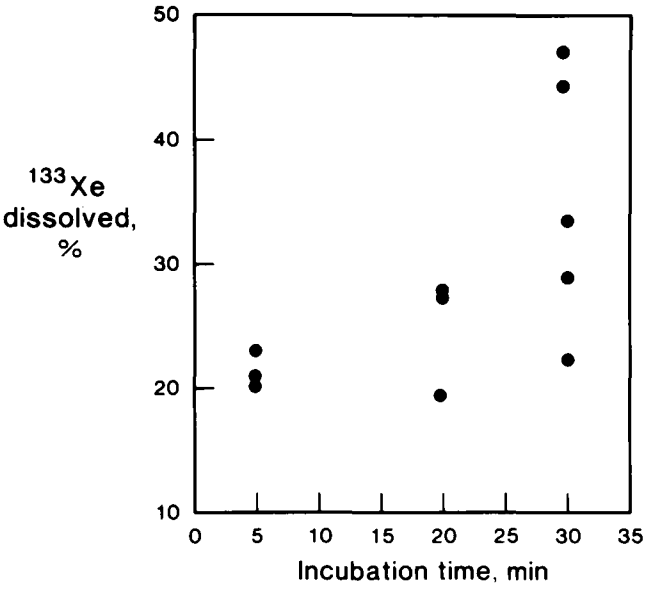

FIG. 1. Effect of incubation time on amount of ^{133}Xe dissolved in isotonic saline at atmospheric pressure and temperature at 4 °C.

Vials of ^{133}Xe gas of different ages (from time of preparation by suppliers) were tested for percentage dissolved to determine the amount of irreversible binding of ^{133}Xe to glass. There was no significant difference (Fig 2).

Storage of ^{133}Xe Gas in Saline

Glass vials were compared to sealed syringes as storage vehicles for ^{133}Xe in saline by monitoring the loss from both receptacles when they were stored in a hood. There was a significant loss of activity from the syringe, whereas in general no loss was found when ^{133}Xe in saline was stored in the original glass vial, even after one or two punctures (Fig. 3). This loss from the syringe is attributed to escape through the barrel fitting of the syringe, because all syringes were capped with

TABLE 1. Effect of Solvent and Temperature on Solubility of Xenon-133

	At 4°C		At 25°C		
Solvent	No. Trials	Amount Solubilized (% ± SD)	No. Trials	Amount Solubilized (% ± SD)	P
Olive oil	3	19.1 ± 7.1	3	14.1 ± 5.0	0.005
Liposyn, 10%	3	18.6 ± 8.4	3	15.0 ± 4.0	0.1
Isotonic saline	5	18.2 ± 4.6	5	24.0 ± 3.0	0.0005
Human serum albumin, 5%	—	—	3	7.5 ± 3.2	—
Human serum albumin, 25%	—	—	4	2.5 ± 3.2	—

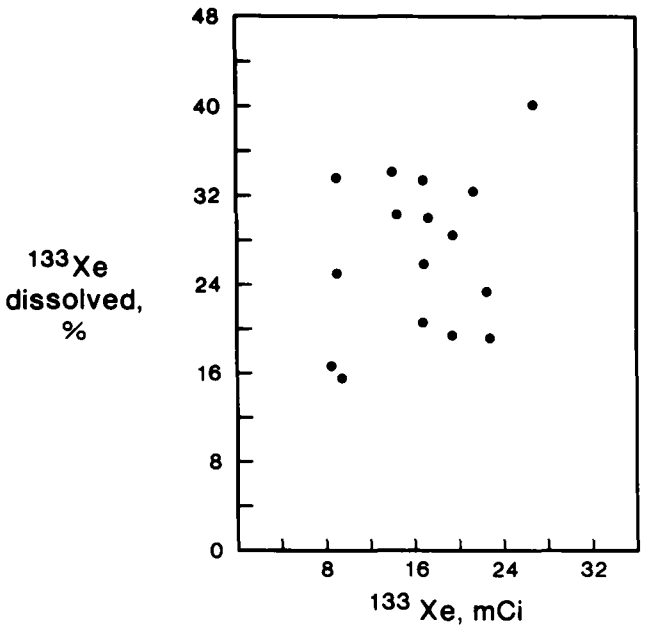

FIG. 2. Solution of ^{133}Xe in isotonic saline at room temperature from ampoules of different ages. The most recent ampoules are those with the highest activity. Ampoules with activities lower than 10 mCi were 1 wk old or older.

a tightly fitting metal seal. The needle and cap should not be considered a sufficient seal for xenon storage.

Xenon-133 Escape from Ampoules

Several punctures of the seal with needles smaller than 20 gauge did not result in increased leakage. However, one or two punctures with a 19-gauge needle did result in leakage.

DISCUSSION

Problems relating to the handling and storage of ^{133}Xe gas in saline were discussed in the literature in the early 1970s, when lung perfusion studies were performed with intravenously injected saline and radiopharmacies had to dissolve ^{133}Xe supplied in ampoules of 1 Ci to prepare multiple doses. Specifically designed stainless steel containers were used to crush the ampoules, and multiple doses with activities of 15–20 mCi per ml of saline were obtained by this procedure (*6,7*). Loss of ^{133}Xe to trapping by various materials has been reported (*8–12*). The uptake by Teflon and polyethylene catheters was found to be 0.5–2% of the dose administered as a bolus. Depending on time of exposure, 5–50% of ^{133}Xe was found to be absorbed by plastic disposable syringes (*8*). In contrast, the loss in glass was only 1%. Trapping of ^{133}Xe in the rubber stoppers of ampoules has been of particular concern: 5 to 18 days after delivery, approximately 80% of the ^{133}Xe was found in the rubber components of the ampoules (*8*). Because lung ventilation studies are now conducted with ^{133}Xe inhalation, the handling of larger doses of ^{133}Xe is not necessary.

For efficiency of solubilization, isotonic saline was found to be the solvent of choice. It is inexpensive, easy to handle, and readily available in sterile form. The dissolving procedure can be performed reliably at room temperature with an efficiency of about 25%. This percentage can be almost doubled by performing the procedure at 4 °C (ice bath) with incubation for 30 min. However, this low-temperature procedure is not used because, in the time between transfer of the preparation to a syringe and injection, the solution generally reaches room temperature. The amount of ^{133}Xe used in our laboratory for intravenous injection can be obtained readily by a room temperature extraction of a standard ^{133}Xe ampoule within its expiration date. In testing skin clearance of ^{133}Xe, a small intracutaneous skin deposit is used and a higher concentration may be desirable. For this reason, the low-temperature extraction may be preferable.

Because of the higher solubility of ^{133}Xe in fatty acids and triglycerides (*13–16*), human serum albumin was tested as a possible solvent. However, all but 1–2% of the fatty acids are removed from commercially supplied albumin in the manufac-

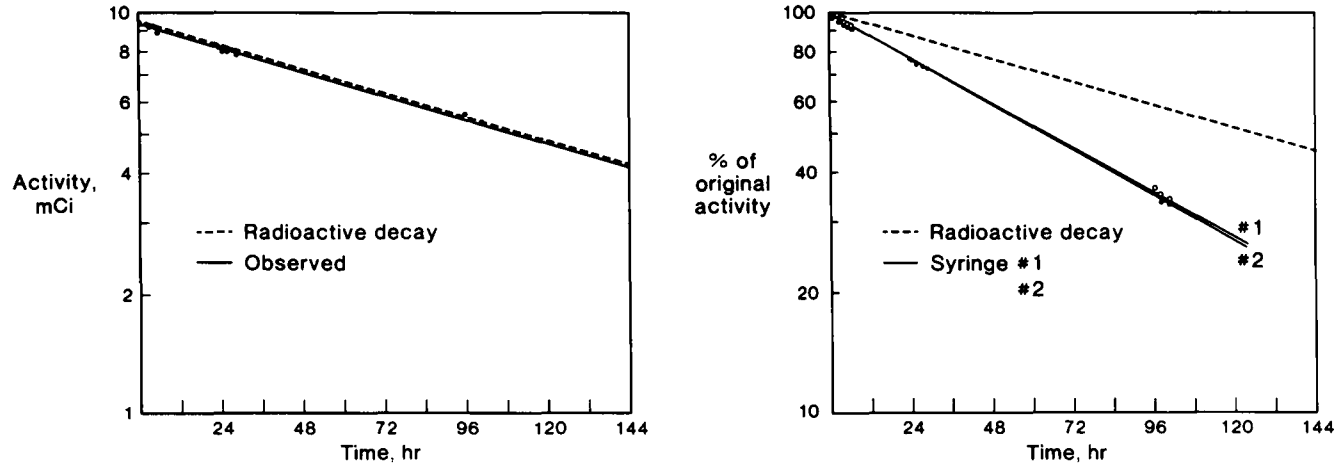

FIG. 3. *Left:* Xenon-133 gas stored in a sealed vial (commercial ^{133}Xe gas vial) showed no escape of ^{133}Xe, and loss of radioactivity was due to normal decay of ^{133}Xe. *Right:* Xenon-133 gas stored in syringes sealed with metal caps showed escape of ^{133}Xe gas with time.

turing process, and this explains the low solubility of ^{133}Xe in albumin solutions.

Olive oil and Liposyn (10%) were also tested because of their lipid content. Olive oil has a high solubility coefficient for ^{133}Xe compared to that of saline (*13,14*), but in this study, it was not a better solvent than saline. This result is thought to be due to a greater loss of ^{133}Xe in drawing a viscous solvent from the ampoule.

The ampoule was the superior container for transporting ^{133}Xe in saline; little or no loss of activity (except decay) was found over a 5-day period. When a syringe was used as a storage device, not only was there significant loss of activity from the syringe but also ^{133}Xe adhered to the plastic material and the amount of this loss was unpredictable. Because of this minimal loss of activity, ^{133}Xe in saline should be transported in the glass ampoule and drawn into a syringe just prior to administration. This prevents uncontrolled leakage of ^{133}Xe into the environment and allows the use of plastic syringes for injection.

It is mandatory that ^{133}Xe in saline be assayed immediately prior to administration because undetected leakage or absorption by the plastic wall of the syringe may significantly decrease the estimated activity by the time it is used. Our data supports a previous study (*8*) which shows that the loss in plastic syringes is less than 5% if the syringe is used only for transfer and not for storage.

The yield of ^{133}Xe in solution did not change when fresh or old ^{133}Xe ampoules were compared. Thus, there is no evidence for increased binding of ^{133}Xe to glass with time. Adsorption not exceeding 1% has been reported (*8*). The seals used for ^{133}Xe ampoules did not show any measurable ^{133}Xe absorption, which is an improvement over previous seals.

Xenon-133 gas in saline prepared by dissolving the commercial gas is not an FDA-approved radiopharmaceutical. Institutions without a broad license will have to acquire an IND for use of this material. Sterility and pyrogenicity tests must also be performed.

The authors believe that exposure to isotonic saline at room temperature for 5 min gives a satisfactory yield of ^{133}Xe in solution for most purposes. About 25% of the activity of ^{133}Xe gas in the ampoules can be extracted. However, yields vary and a direct assay of activity prior to the injection is recommended. Xenon-133 gas may escape even in circumstances in which water is well contained (i.e., sealed syringes). A syringe needle no larger than 20 gauge should be used, and the number of perforations should be kept at a minimum.

FOOTNOTE

* New England Nuclear, Inc., North Billerica, MA.

ACKNOWLEDGMENT

Presented in part at the 30th Annual Meeting of The Society of Nuclear Medicine, Technologist Section, St. Louis, MO, 1983.

REFERENCES

1. Moore WS, Henry RE, Malone JM, et al. Prospective use of xenon Xe-133 clearance for amputation level selection. *Arch Surg* 1981;116:86–88.

2. Silberstein EB, Thomas S, Cline J, et al. Predictive value of intracutaneous xenon clearance for healing of amputation and cutaneous ulcer sites. *Radiology* 1983;147:227–29.

3. Kuikka J, Ahonen A, Koivula A, et al. An intravenous isotope method for measuring regional cerebral blood flow (rCBF) and volume (rCBV). *Phys Med Biol* 1977;22:958–70.

4. DiPiazza HJ, Harbert JC. Preparation of sterile xenon-133 in saline for tissue perfusion studies. *J Nucl Med* 1983;24:1070–71.

5. Suzuki A, Suzuki MN, Weis AM. Analysis of a radioisotope calibrator. *J Nucl Med Technol* 1976;4:193–98.

6. Carroll RG, Berke RA, Anger RT, et al. A multiple-dose ^{133}Xe solution "generator": The disposable glass ampule equilibration chamber. *J Nucl Med* 1973;14:935–38.

7. Bulkley GB, Gharagozloo F, Alderson PO, et al. Use of intraperitoneal xenon-133 for imaging of intestinal strangulation in small bowel obstruction. *Am J Surg* 1981;141:128–35.

8. Ponto RA, Kush GS, Loken MK. Consideration of problems in handling and radiation dosimetry of ^{133}Xe. *J Nucl Med* 1970;11:352(A).

9. Keaney J, Liuzzi A, Freedman GS. Large dose errors due to redistribution of ^{133}Xe in carpules and plastic syringes. *J Nucl Med* 1971;12:249–50.

10. LeBlanc AD, Johnson PC. The handling of xenon-133 in clinical studies. *Phys Med Biol* 1971;16:105–9.

11. Ponto RA, Loken MK. Radioactive gases: Production, properties, handling, and uses. In *Radiopharmaceuticals*. G. Subramanian, BA Rhodes, JF Cooper, et al. (eds), New York: The Society of Nuclear Medicine, 1975:296–304.

12. Abdel-Dayem HM. Handling of radioactive ^{133}Xe dissolved in saline. *J Nucl Med* 1972;13:231(L).

13. Kitani K. Solubility coefficients of ^{85}krypton and ^{133}xenon in water, saline, lipids, and blood. *Scand J Clin Lab Invest* 1972;29:167–72.

14. Yeh S-Y, Peterson RE. Solubility of carbon dioxide, krypton, and xenon in aqueous solution. *J Pharm Sci* 1964;53:822–24.

15. Ladefoged J, Andersen AM. Solubility of xenon-133 at 37 °C in water, saline, olive oil, liquid paraffin, solutions of albumin, and blood. *Phys Med Biol* 1967;12:353–58.

16. Yeh S-Y, Peterson RE. Solubility of carbon dioxide, krypton, and xenon in lipids. *J Pharm Sci* 1963;52:453–58.