Radiation Exposure to Human Trachea from Xenon-133 Procedures

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The general dosimetry of ^{133}Xe for human studies is well documented, but the resultant radiation exposure to tracheal tissue is poorly known. This organ is of central relevance because the tracer is primarily eliminated through exhalation. **Methods:** We report actual ^{133}Xe concentrations in respiratory air during measurement of regional cerebral blood flow (rCBF), when the tracer is administered both by inhalation and intravenous injection. Data were collected from 102 patients, with equal gender representation and an age range of 18–82 yr. Most of the patients had subarachnoid hemorrhage or Alzheimer's disease or were normal control subjects. Average administered doses were 18 ± 4 mCi by inhalation and 15 ± 3 intravenously. **Results:** We found average respiratory concentrations of about 1.80 mCi/liter during a 1-min inhalation and 0.74 mCi/liter following intravenous injection of standard doses. These activities drop rapidly: average respiratory concentrations during the second minute are 0.70 mCi/liter for inhalation and 0.19 mCi/liter for intravenous injection and reach negligible levels thereafter. We calculate that the tracheal absorbed dose from ^{133}Xe procedures is approximately 28 mrad following inhalation and about 11 mrad following intravenous injection. These values reflect the full 11-min exposure, but most of the activity is only present initially. **Conclusion:** These values will agree with previous estimates and indicate an excellent safety margin.

Key Words: radiation exposure; dosimetry; xenon-133; regional cerebral blood flow

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Planar lung and brain perfusion studies have widely used ^{133}Xe, and there is now renewed interest in this tracer for quantitative brain SPECT imaging. Although the radiation exposure from ^{133}Xe is extensively studied and amply documented, the target organ has traditionally been considered to be the lungs. In fact, the most recent and authoritative publication on radiation exposure from radioxenons does not even mention the trachea among the exposed organs (*1*). Yet the trachea is inevitably exposed, as xenon is principally eliminated by exhalation. Further, when xenon is administered by inhalation, as is commonly done, tracheal tissue is even more affected. Therefore, this tissue must be considered when calculating radiation exposure.

To provide an estimate of radiation exposure, we reviewed the previous literature, measured actual concentrations of ^{133}Xe in respiratory air from our own data, using both intravenous and inhalation administration routes, and calculated absorbed doses.

METHODS

Subjects

This analysis is based on patients and healthy control subjects participating in measurements of regional cerebral blood flow (rCBF) with ^{133}Xe; 51 were administered the tracer by inhalation and 51 intravenously. The total age range was 18–82 yr, and the main diagnoses were subarachnoid hemorrhage and Alzheimer's disease. A few patients had sickle cell disease and major depression and other psychiatric disorders.

When inhaled, ^{133}Xe was administered from the Cerebrograph 32c (Novo Diagnostic Systems, Hadsund, Denmark), an instrument that accepts and stores large quantities in an internal, heavily shielded storage tank. Small doses for each procedure are transferred by built-in pumps to the internal spirometer, which contains sensors and indicators for total volume and ^{133}Xe concentration. These indicators were recorded before and after each procedure; the difference between them is the administered dose.

When administered intravenously, injectable ^{133}Xe was prepared by crushing, under sterile conditions, a commercially supplied gas ampule and dissolving the gas in saline. Individual doses were drawn into a lead-shielded glass syringe before the injection and were dose-calibrated before and after injection. The difference provides the dose actually administered.

All counts in this experiment were derived from a built-in detector, usually termed the "air detector," of the Cerebrograph 32c. This contains a 3/4-in. D × 3/4-in. H NaI(Tl) crystal as a scintillation phosphor, a photomultiplier tube and a voltage divider chain. A 5-mm lead-shielded stainless steel helix encloses the scintillation crystal, and the sampled air circulates through the helix tubing. The internal spirometer of the Cerebrograph 32c provides a reading in millicuries per liter, and its detector is calibrated monthly against both ^{133}Ba and ^{133}Xe. This detector, however, can be read only in units of millicuries per liter during

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calibration. During actual patient scanning, the detector produces activity only in units of counts. In this project, we collected samples of respiratory air and measured their activity each 312.5 msec during uptake. To calibrate the relationship between these counts and ^{133}Xe concentration in millicuries per liter, the observed counts were plotted against concentrations and a least squares fit determination was made. The best straight line ($r = 0.992$, $p < 0.0001$) indicated that the concentration in millicuries per liter could be well approximated by multiplying the observed counts (integrated over 312.5 msec) by $0.5331 \cdot 10^{-3}$. In other words, the correction factor in standard units is 0.167 mCi/liter/kcps.

Having determined actual respiratory concentrations, we recalculated absorbed dose estimates. As was previously done in MIRD Dose Estimate Report No. 16 (*2*), we assumed that the relevant exposed volume consists of a 2-mm thick layer, including epithelial and glandular tissue. Dose (D) was calculated by the Electron Gamma Shower program (*3*), a coupled photon-electron Monte-Carlo transport code, using the appropriate beta spectrum:

$$D/Q = 4.57 * 10^{-11} \text{ Gy cm}^3/\text{Bq sec}, \qquad \text{Eq. 1}$$

where D/Q is the ratio of absorbed dose to cumulative activity, and

$$D = (D/Q) * c * 37 * 10^6 \text{ Bq} * t \text{ sec}/1000 \text{ cm}^3$$

$$= c * t * 169.09 * 10^{-8} \text{ Gy}, \qquad \text{Eq. 2}$$

where c is airway concentration in millicuries per liter, and t is exposure time in seconds.

Data Analysis

To trace actual tracheal concentrations, we analyzed several variables. An administered dose was computed as the difference between initial and final total activity in the syringe or spirometer bag. Mean concentration in respiratory air was obtained as follows as a function of time. Patients wore a face mask during the procedure. The air inside the mask was continuously sampled by a pump at 1.5 liters/min, and the air sample was drawn through the metal helix in front of the air detector, which sent the information through the usual nuclear electronics channel, where readings were integrated every 312.5 msec. These counts were continuously read by a computer, which then created the so-called "air curve." A typical example of this curve is shown for inhalation and intravenous administration in Figure 1.

On this curve, which describes the continuous changes of ^{133}Xe concentration in respiratory air, we defined the "average air curve." This was obtained by averaging the 16 readings obtained in each 5-sec period (Fig. 1). The values of this average respiratory concentration were further averaged during the first and second minute as well as for the whole 11-min clearance time. The highest, initial respiratory concentration was also defined, as well as the highest arterial concentration achieved. The first value corresponds to the first breath and is largely determined by the dose administered. The latter value is identical to the first breath with intravenous administration but corresponds to the highest end-tidal point by inhalation, usually occurring at the end of the equilibration minute. Finally, we defined the integral over all 11 min of the end-tidal curve, which corresponded to arterial concentrations, as total brain input, including initial dose and recirculating tracer.

Comparisons between the two patient samples (inhalation versus intravenous) were performed with unpaired Student's t-tests for means (two-tailed) and F ratios for variances.

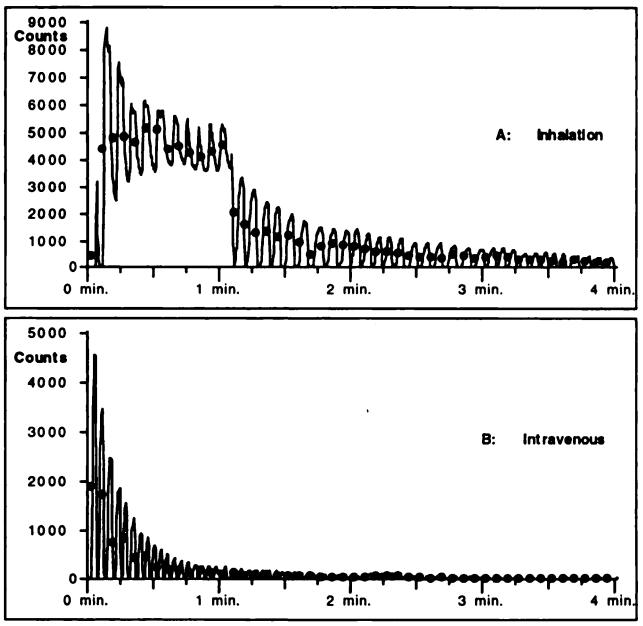

FIGURE 1. Continuous recording of ^{133}Xe concentration in respiratory air: (A) after closed-circuit inhalation and (B) after bolus intravenous injection. Mean respiratory activity is denoted by closed circles.

TABLE 1
Findings from Two Administration Routes (n = 51 Patients Each) and Their Differences by Student's t-Tests

Variable	Inhalation	Intravenous	Significance (p)
Age (yr)	46 ± 25	49 ± 15	ns
Dose (mCi/liter)	17.6 ± 3.9	15.1 ± 2.6	<0.001
First-minute average respiratory activity (mCi/liter)	1.80 ± 0.36	0.74 ± 0.34	<0.0001
Second-minute average respiratory activity (mCi/liter)	0.70 ± 0.21	0.19 ± 0.13	<0.0001
Whole run average respiratory activity (mCi/liter)	0.25 ± 0.05	0.10 ± 0.04	<0.0001
Whole run in first minute (%)	65.3 ± 8.2	66.5 ± 12.7	ns
Whole run in first 2 min (%)	90.1 ± 4.3	83.2 ± 8.4	<0.0001
Maximum respiratory activity (mCi/liter)	3.81 ± 0.48	2.83 ± 1.16	<0.0001
Maximum arterial activity (mCi/liter)	2.00 ± 0.53	2.83 ± 1.16	<0.0001

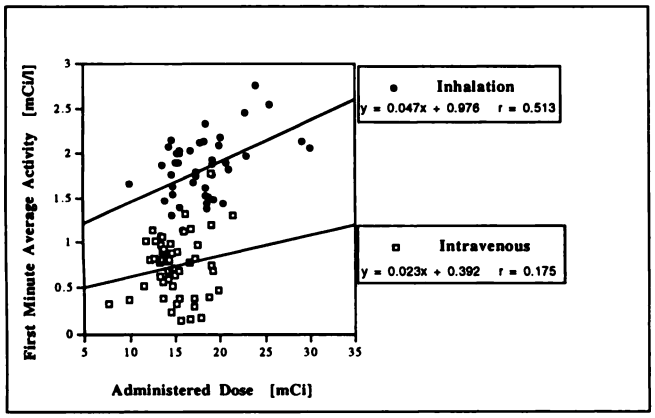

FIGURE 2. Average ^{133}Xe concentration in respiratory air during the first minute of closed-circuit inhalation (open circles) and following bolus intravenous injection (open squares). Respiratory activity is higher during inhalation and better correlated with administered dose.

RESULTS

All comparisons between the two administration routes are detailed in Table 1. The two patient groups (inhalation versus intravenous) were well-matched for age (t_{100} = 0.75; ns), although the age variance was significantly greater with inhalation ($F_{50,50}$ = 2.73; $p < 0.001$). The groups were also gender-matched (25 women, 26 men), although women were significantly older than men (60 ± 17 versus 34 ± 16; $F_{1,98}$ = 116; $p < 0.0001$). The administered dose by inhalation was slightly but significantly higher than the intravenous dose (t_{100} = 3.75; $p < 0.001$); dose variance was also significantly higher by inhalation ($F_{50,50}$ = 2.32; $p < 0.01$).

Generally, respiratory concentrations were higher for inhalation than intravenous administration (Table 1). Age was not significantly associated with any of the relevant variables, despite the full age range examined here (18–82 yr). Administered dose, as expected, was significantly correlated with several variables. Those correlations, however, were of moderate magnitude. The largest correlations, and of greatest importance for this article, were obtained between dose and the average respiratory concentration during the first minute. These regressions are shown in Figure 2. The overall correlation was 0.49. The correlation for intravenous administration was low and nonsignificant; the correlation for inhalation was more robust.

The average tracheal activity over the full 11-min clearance was determined to be 0.25 ± 0.05 and 0.10 ± 0.04 mCi/liter for inhalation and intravenous administrations, respectively. By inserting these activity levels and the time of 660 sec into Equation 2, the dose estimate becomes $2.79 * 10^{-4}$ Gy for inhalation and $1.12 * 10^{-4}$ Gy for intravenous administration. In traditional units, these values are about 28 and 11 mrad, respectively. These numbers, however, slightly overestimate exposure due to the assumption of linearity inherent in averaging. As Table 1 indicates, most of the activity occurs during the first 2 min, with average concentrations of about 1.25 and 0.465 mCi/liter. These values result in absorbed dose estimates of about 25 and 9 mrad, respectively.

DISCUSSION

Naturally, actual ^{133}Xe concentration and exposure levels depend upon administered dose as well as the route of administration and tracer kinetics. In our laboratory, the spirometer is usually loaded for inhalation with about 5 mCi/liter in a volume of about 6 liters for a total activity of about 30 mCi. Slightly more than half this activity (about 18 mCi) is actually taken up by the patient following equilibration of the spirometer with alveolar volume. This dose is similar to the dose we usually use for intravenous administration, about 15 mCi.

Although administered doses are similar by the two routes, respiratory concentrations are quite different, as expected, due to divergent kinetics. Initial respiratory concentration peaks during the first breath. This corresponds to the highest arterial concentration after intravenous administration, reflected in the highest end-tidal exhalation, about 2.8 mCi/liter in this study. For inhalation, this first breath reflects respirator concentration diluted by laryngeal volume, about 3.8 mCi/liters in this study. After intravenous bolus injection, both respiratory and arterial concentrations drop rapidly. In contrast, they are fairly constant during the 1 min of closed-circuit inhalation and then drop more slowly. Consequently, respiratory concentrations are substantially lower after intravenous administration.

Radiation exposure to tracheal tissue has been estimated in only three previous reports. According to Lassen (*4*), a standard ^{133}Xe inhalation procedure (1 mCi/liter spirometer concentration) would result in about 100 mrad tracheal exposure (compared to only 18 mrad to lung). Goddard and Ackery (*5*) also assumed a spirometer containing 1 mCi/liter ^{133}Xe in oxygen. After total exhalation to residual volume, the subject inhales to maximal lung capacity and holds his breath for 30 sec. Rebreathing follows for 3 min; no dilution of spirometer concentrations occurs, and the washout from healthy lung is assumed to have a 30-sec half time. In their calculations, assuming the rates for washin and washout to be equal, dose is linearly related to spirometer concentration and rebreathing time. Therefore, their values for tracheal absorbed radiation corrected for 1 min of rebreathing of 1 mCi/liter is about 200 mrad. The discrepancy in tracheal mucosa exposure between these authors and Lassen (*4*) is due to calculation of beta absorption in 5 μm thickness, whereas, Lassen (*4*) computed the mean dose to a 100-μm layer.

Finally, the newest study was conducted by Powell et al. (*6*) and unfortunately is published only in abstract form. These authors used a phantom and estimated 5 rad/hr for rebreathing of 1 mCi/liter concentration. Our data document that respiratory concentrations reach equilibrium

with spirometer concentrations, under most circumstances, at the end of a 1-min rebreathing, and then decline rapidly, essentially to negligible values within the next 60 sec. A concentration of 1 mCi/liter would result in exposure of about 83 mrad/min. This is lower than, but reasonably close to, the older estimates (*4,5*).

Our current data show that average respiratory concentrations during a 1-min inhalation are about 1.80 mCi/liter and only 0.74 mCi/liter following intravenous injection of standard doses. Both show a weak-to-moderate relationship to dose. This 1-min exposure is about 66% of the total exposure incurred during an 11-min procedure because respiratory concentrations drop rapidly after the first minute. The average respiratory concentrations during the second minute are 0.70 mCi/liter for inhalation and 0.19 mCi/liter for intravenous administrations. The first 2 min account for 90% of the inhalation exposure and 83% of the intravenous exposure. The averages over the entire 11 min are 0.25 mCi/liter and 0.10 mCi/liter. Therefore, the phantom studies by Powell et al. (*6*) are reasonably accurate. We have obtained even lower absorbed dose estimates due to a lower observed respiratory concentration and the Electron Gamma Shower (EGS4) calculation (*2*).

CONCLUSION

Tracheal exposure from ^{133}Xe procedures is approximately 28 mrad following inhalation and about 11 mrad following intravenous injection. These values reflect the full 11-min exposure, but most of the activity is only present initially. These values are well within accepted safety limits and do not change the overall risk/benefit calculation derived from MIRD Report No. 9 (*1*), since they leave the lungs as the target organ.

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