Biodistribution and Kinetics of Nasal Carbon-11-Triamcinolone Acetonide

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PET is a technique with a strong potential for use in drug evaluation and development. In particular, the distribution and pharmacokinetics of locally administered drugs may be advantageously explored noninvasively using labeled compounds. This pilot study was performed to demonstrate the effectiveness of PET for drug development and to determine the human biodistribution and kinetics of triamcinolone acetonide, labeled with ^{11}C, formulated and nasally administered as Nasacort® AQ nasal inhalant. **Methods:** Carbon-11-labeled triamcinolone acetonide was formulated as the commercial product, and PET scans of the heads of four volunteers were performed in a vertical orientation. Region-of-interest analysis with MRI coregistration was used to analyze the distribution and kinetics in nasal tissues. **Results:** Deposition of the majority of the dose on target tissues was immediate. Penetration into sinuses was observed. There was moderate redistribution and slow migration of the drug through nasal passages to the throat. Significant amounts of the drug remained in target regions for several hours. **Conclusion:** PET is an effective means to determine local drug distribution and kinetics.

Key Words: PET; inhaler; nasal; biodistribution; steroid

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Measurement of the parameters of drug delivery and pharmacokinetics in human subjects is one area in which nuclear imaging techniques have significant untapped potential. This activity is not directly related to patient care, but the technique may eventually benefit a large number of patients. The benefits of nuclear imaging to drug development arise from the rapid, objective and relatively inexpensive supply of data concerning the distribution and action of a drug of interest. The data can be used to speed and guide drug development. Benefits may include a reduction in the effort of discovery of desirable or undesirable properties that may lead to development or abandonment of drugs. It is relatively straightforward to use nuclear medicine techniques to measure physiological responses to administered drugs. Such studies determine the degree and duration of a drug's physiological effect and objectively assess its effectiveness in treatment. Often, a small subject sample and a shortened time are required, as compared to the classic methods of clinical trials. A different and equally useful type of information can be obtained by measuring the distribution and kinetics of the drug itself. Typically, the concentration of an administered drug and its major metabolites can be measured in plasma and excreta without using radiolabels. However, it is generally not practical to directly determine rates of absorption and the concentration of the drug at the targeted sites of action. These values are inferred, if possible, from serial plasma sampling, or they may remain completely unknown despite their importance in the achievement of desired therapeutic effects.

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If a drug of interest can be radiolabeled, important parameters of its biodistribution and pharmacokinetics can be measured directly using techniques that are common in nuclear medicine. When the therapeutic effect of the drug relies on local action in a specified tissue, biodistribution and pharmacokinetic information can be essential to document the mechanism of action and clinical efficacy of the drug. A locally applied corticosteroid is a good example of a drug that lends itself to effective evaluation using nuclear medical techniques.

Local administration of drugs is commonly used to enhance desirable regional effects while reducing toxic or other undesirable side effects that can result from systemic administration and associated delivery to nontarget organs. It is an effective alternative for airway, dermatologic and anesthetic drugs. In particular, drugs that are targeted for effect in the nasal passages, including vasoconstrictors, cromolyn and corticosteroids, generally are locally administered by nasal inhalation (*1,2*). Triamcinolone acetonide (TAA) is a potent anti-inflammatory synthetic glucocorticoid that is topically administered in several forms (*3–6*). For treatment of rhinitis, TAA has been formulated as a metered-dose inhaler (Nasacort®) and, recently, has been formulated as a thixotropic aqueous solution administered by a metered-dose atomizer (Nasacort® AQ). The thixotropic formulation is a viscous liquid that is designed to decrease in viscosity during atomization and then increase in viscosity after deposition on the mucosa. The purpose of this study was to examine the properties of the aqueous formulation of TAA. This is intended to enhance the retention of the active ingredient at the target tissues in the nose. To determine whether the drug is effectively delivered to the target tissues and to measure its retention on various anatomic structures, this study was undertaken as a collaborative pilot project by Rhône Poulenc Rorer (RPR), the manufacturer of the product, and the PET facility at Case Western Reserve University/University Hospitals of Cleveland. Although planar imaging, SPECT and PET all come to mind as potential tools for measuring biodistribution and kinetics, in this case, only PET was a viable candidate. The need was to determine not just initial spray pattern but whether the drug remains on the target tissues, which depends on the solubility and absorption characteristics of the drug molecule. Even different steroids behave differently, so a tracer that is not identical to the drug molecule would not behave in the same way. The molecule contains only carbon, hydrogen, oxygen and fluorine. Therefore, chemically, PET was the only possibility, aside from its advantages in quantitation and resolution. This study was expected to clearly measure the effectiveness of the delivery method, to allow the regional pharmacokinetics of the drug to be related to its clinical efficacy and to aid the evaluation of the thixotropic formulation. This study was also intended as a demonstration project to explore the feasibility and benefits of the application of PET to drug evaluation and design.

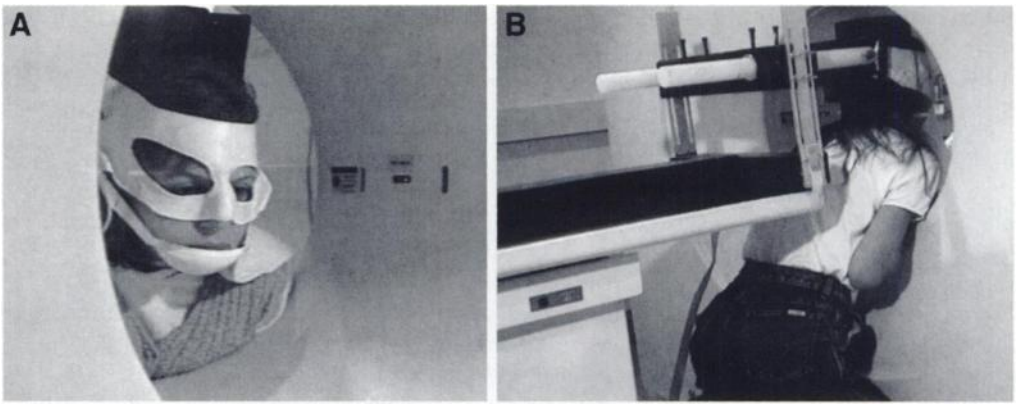

FIGURE 1. Positioning and support device used for vertical-face portion of PET data acquisition. (A) Face view through back of camera. (B) Support apparatus from front of camera.

MATERIALS AND METHODS

Subjects

Four normal healthy female volunteers (age range 22–27 yr; weight range 48–65 kg) were recruited for the study. The apparent sex and age grouping of the volunteers was a random occurrence and did not result from enrollment criteria. Inclusion criteria were age of 18–50 yr and normal nasal mucosa. Exclusion criteria were: body weight >15% above or below the ideal body weight, as specified by Metropolitan Life tables; previous history of chronic disease of the upper or lower airway; any smoking within the past 2 yr or a smoking history of >10 pack-yr; history of significant cardiovascular, neurological, hepatic, renal or respiratory conditions; history of any other condition deemed by an examining physician to potentially interfere with the study; clinically relevant deviations from normal or evidence of drug abuse on general physical examination or laboratory test (Chem23, complete blood count with differential or urinalysis); and hypersensitivity to corticosteroids. Postadmission exclusion criteria were development of illness and use of medications that could affect the nasal mucosa, airways or respiratory function.

Study Protocol

The protocol, including recruitment procedures and materials, radiopharmaceutical preparation, study procedures and the informed consent form, was approved by the University Hospitals of Cleveland Institutional Review Board and Radioactive Drug Research Committee. Prospective volunteers gave written informed consent and underwent screening, consisting of a physical examination and blood and urine laboratory tests. Accepted volunteers were trained in the use of the Nasacort® AQ inhaler using a placebo inhaler provided by RPR. Training in coordinated drug administration (using placebo) by a research nurse was included because the volunteers were not able to self-administer while positioned in the PET scanner. PET scans were then performed as described below. After the PET scans, a MRI scan of the head of each volunteer was obtained.

PET Scanning

The scans were obtained using the 47-slice EXACT scanner (Siemens Medical Systems, Inc., Iselin, NJ) at University Hospitals of Cleveland in two-dimensional mode. The PET scan was performed in two parts. The second part conformed to typical scan practice with the volunteer in the supine position and the head fixed using a standard head holder that incorporated a thermoplastic face mask. However, there was a concern that gravity-induced experimental artifacts could arise from supine administration of the aqueous solution. Therefore, the first part of the scan was performed with the volunteer's head in a nearly vertical orientation. This orientation was achieved by positioning the volunteer in a modified kneeling position in front of the scanner.

An apparatus (Fig. 1) was constructed to comfortably support the weight of the volunteer and to support the head and restrict its motion during the scan. The apparatus was constructed to fit the small available space between the fixed scanner bed and the scanner. The device consisted of a frame-mounted adjustable bicycle seat to support the majority of the volunteer's weight and was fitted with knee pads to make the kneeling position more comfortable. Volunteers simultaneously kneeled on the pads and sat on the bicycle seat while leaning forward onto the edge of the camera opening and into the field of view. The seat was adjusted to allow the head to reach comfortably into the center of the field of view. A curved and padded head-holder was mounted vertically on a second frame that was fixed firmly to the movable scan bed. The head holder was centered laterally on the field of view, was vertically adjustable and could be adjusted horizontally by moving the scan bed toward or away from the camera. After the head holder was firmly positioned to support the back of the volunteer's head, a thermoplastic face mask (Smith & Nephew, Germantown, WI; 15 × 45 cm with eye and ear holes) was molded over the face and clamped to the head holder. The mask was carefully molded before hardening to ensure that the nasal passages were not constricted. Further support was provided by a chin strap that was clamped to the frame and tightly adjusted to hold the weight of the head. A larger (75 × 45 cm) piece of thermoplastic was then molded over the upper back, shoulders and neck of the volunteer. This "collar piece" did not contribute to support or positioning during the vertical PET scan, but was later used as an aid to reproduce the neck curvature during the supine PET and MRI scans.

The volunteer was first positioned in the camera with the tip of the nose at the far edge of the field of view and the head centered in the xy plane of the camera. The support apparatus was adjusted to optimize the volunteer's comfort and position. The volunteer and the apparatus were then marked using laser positioning aids, and a transmission scan of the head was obtained (15 min using the camera's internal rotating ^{68}Ge source). At the conclusion of the transmission scan, the volunteer was released from the apparatus and allowed to relax. Just before delivery of the radiopharmaceutical, the volunteer was repositioned in the scanner. The drug canister was weighed (Mettler balance, 0.0001-g precision) and assayed for radioactivity (Capintec dose calibrator; Capintec, Inc., Ramsey, NJ) before and after administration of the dose. Scan data acquisition was started immediately before the intranasal administration of the dose. The administration was performed by the research nurse who had trained each volunteer. Positioning and administration were coordinated using verbal cues between the volunteer and nurse according to the previously practiced procedure. The volunteer began to inhale vigorously through one nostril before the actuation of the canister and continued the inhalation until after the actuation in that nostril was complete. Thirty seconds after the administration in one nostril, the sequence was repeated in

the other nostril. This was representative of the procedure and the maintenance dosage for treatment of allergic rhinitis as described in the package insert, one actuation (55 μg, ~0.1 g) per nostril once per day.

Scan data were collected using a 32-frame, 120-min dynamic acquisition. The acquisition was divided into time frames as follows: 12 × 10 sec, 3 × 1 min, 5 × 2 min, 6 × 5 min, 3 × 10 min and 3 × 15 min. The time at which the acquisition in the vertical orientation ended was determined by each volunteer's estimation of her ability to remain in the supported kneeling position. Whenever possible, this was performed at the end of a programmed time frame. If the volunteer was removed from the field of view in midframe, she was not repositioned until the following frame had begun to acquire data, to avoid corruption of the data previously acquired. The PET camera's data acquisition was not interrupted, but the volunteer was taken out of the camera, the restraints and support apparatus were removed and the standard scan bed surface and head holder were replaced. This process required less than 2 min. The volunteer was then repositioned in the supine position in the camera, using the previously formed collar piece, and data acquisition was continued for the remainder of the 120-min scan period. The time that the volunteer spent out of the field of view was measured, and the resulting shortening of the acquisition time during the affected frame was considered during data analysis. A second transmission scan (15 min) was performed while the volunteer remained in the supine position at the conclusion of the data acquisition.

Radiopharmaceutical

The ^{11}C radiolabeling and purification of TAA, the active ingredient of the formulation, were reported previously (*7*). Briefly, the labeling process consisted of the reaction of ^{11}C-labeled acetone with triamcinolone to produce the acetonide, which was then purified by high-performance liquid chromatography. The labeled compound is quite stable, remaining unchanged for several hours at least. A small quantity of the labeled drug was mixed into the commercial preparation, while maintaining the manufacturer's release specifications.

The commercial formulation, Nasacort® AQ, was kindly provided for the study by RPR. The solution was transferred to a sterile stock bottle for formulation of the labeled product. The bottle and spray pump were emptied of product and used to receive and administer the labeled product. After synthesis and high-performance liquid chromatography purification, the solvent was evaporated from ^{11}C-TAA. Nasacort® AQ (1.5–5 ml) was added to the dry vial and warmed and agitated for 30 sec to dissolve the labeled TAA. The volume used was determined by the amount of radioactive product present. A portion of the resulting labeled solution was further diluted with unlabeled stock solution, if required, to achieve the desired concentration of radioactivity. The volumes and dilutions were chosen such that a 1.5-ml portion of the final labeled solution was added to the administration bottle, containing a total of no less than 0.150 mCi and no more than 1.125 mCi at the time of administration of the dose to the volunteer. The 1.5-ml volume was chosen because it was the smallest volume sufficient to ensure that a complete dose would be delivered regardless of the angle at which the canister was held. After the dose was added to the bottle and the spray pump was attached, two full actuations were sprayed into an absorbent pad to ensure that the actuator was filled with labeled drug. The dose was then delivered to the scan room and administered by the study nurse.

MRI Scanning

The MRI scans were obtained using a Magnatome SP scanner (Siemens Medical Systems, Inc.) with an MP-RAGE sequence with 10° flip angle, 11.5-msec repetition time, 5-msec echo time, 300-msec T1, an effective slice thickness of 1.25 mm and 128 three-dimensional partitions. The entire head and part of the neck were scanned using a 24-cm field of view. The molded collar piece that was made during the PET scan was placed for the MRI scan as it was for the supine PET scan. Three-dimensional image data were reconstructed to a resolution of 2 × 2 × 2 mm voxels and stored as a single-volume set of data.

Image Analysis

Data reconstruction and manipulation was performed on a network of computers using programs and algorithms that were developed for the purpose. PET data from the transmission scans were reconstructed to form images representing tissue density. The transmission images were then aligned with the MRI scan so that the PET and MRI images could be superimposed. The alignment was performed in six degrees of freedom using a combination of manual methods and the technique described by Woods et al. (*8*). The accuracy of the image registration was within 1 mm. Emission images from the vertical orientation segment of the PET scan were reconstructed with attenuation correction using the measured attenuation values from the transmission image. Camera calibration factors were applied so that the emission PET data were expressed in μCi/ml of body volume and decay corrections were made to the time of administration from the midpoint in time of each scan. The reconstructed PET emission images did not contain sufficient anatomic cues to allow independent alignment, and so they were subjected to the same transformations as the PET transmission image to align them with the MRI scan. Because of the length of the study, some motion was detected between emission scans in certain time sequences. Small corrections were applied to these images by comparing and reregistering them to the initial emission image of the same time sequence.

The supine orientation images were attenuation corrected somewhat differently. The transmission scan from the end of the scan sequence was reconstructed as an image. This image was used for image registration of emission images from the supine orientation with MRI, as was done for the scans in the vertical orientation. The transmission scan was of sufficient quality for the purposes of image registration, but because radiopharmaceutical was present during the final transmission scan and because the scan was deliberately short, it was not suitable for use in attenuation correction. Therefore, the initial transmission scan of the head was aligned to the final one. A new transmission sinogram was then calculated from the reoriented transmission data from the first transmission scan. It was this sinogram that was used for the attenuation correction of the supine position scans before coregistration with the MRI scan.

An additional correction was applied to the data from any time frame during which the volunteer was being moved between the two scan positions. The time during which data were acquired in such frames was less than the full acquisition time of the frame. The resulting calculated activity concentration, therefore, had to be increased by the ratio of the nominal acquisition length of the frame to the actual time during which the head was in the field of view.

After image reconstruction and alignment, the reconstructed PET slice data (from the 47 slices obtained by the EXACT unit having axial resolution of 2.0 mm and transaxial resolution of 3.375 mm) were interpolated by the cubic spline method to generate a three-dimensional volume set composed of 2-mm^3 voxels for superimposition onto the MRI image. Regions of interest were then defined to include the entire volume that could contain radioactivity in any of the scans acquired during the study.

Data Analysis

The 104 small cubic regions were grouped into larger anatomically relevant three-dimensional regions according to their location on the MRI image. Those regions were frontal sinus, ethmoidal sinus, maxillary sinus, sphenoidal sinus, pharyngeal recess, oropharynx, superior turbinate, inferior turbinate, vallate papillae, soft palate, pterygoid process, styloglossus, lingual tonsil, epiglottis, esophagus, thorax, tongue, lip and the tip of the nose. The anatomic assignments of the regions were made by an experienced nuclear medicine physician. The PET radioactivity data were decay corrected to the time of dose administration. It was then converted using the measurements of administered dose (activity and drug mass) to represent the total drug mass present in each region of interest. These data were plotted as time–dose curves of the percentage of administered dose for each anatomic region group. The decay-corrected PET (dose distribution) data were also displayed visually as an image overlay of time-dependent PET data on the whole-head MRI image from various angles of view. The resulting images could be viewed singly or grouped as a cine display showing a rotating head, changing frame of reference and/or time-lapse display of the drug administration and subsequent movement and clearance.

RESULTS

The first volunteer studied in this series demonstrated the pilot nature of the work. There was a series of technical problems, beginning during radiopharmaceutical production and formulation and continuing to include unanticipated motion during the PET scan and difficulties in data analysis. The problems were all identified and corrected before additional studies were performed. Although the data obtained from the first study were useful and consistent with the other studies qualitatively, motion of the head during PET scanning made it impossible to complete the quantitative analysis of the study. Differences between the first study and the others will be noted below. Quantitative conclusions drawn concerning the properties of the pharmaceutical are based on data from the last three volunteers.

The canister for dose administration contained 1.5 ml of a 0.055% TAA solution or 825 μg of TAA. Because the TAA labeling process requires added carrier (*1*), the initial labeled product had a relatively low specific activity range of 0.1–1.6 Ci/mmol. The total mass of TAA present in the labeled product at the end of synthesis was 65 μg (0.15 mmol). The amount of mass that was added to the Nasacort® AQ canister varied with the percentage of the radioactivity that was needed to achieve a nominal concentration of 1.5 mCi/ml. The mass of TAA added to the canisters for the second through fourth volunteers was 1.7–3.6 μg, but for the first volunteer, it was 65 μg. The addition of labeled product, therefore, increased the concentration of TAA in the first dose by 7.8% over the commercial preparation, but remaining doses were increased by <1%. The Nasacort® AQ product was not otherwise altered by labeling of the TAA. Volunteers received 212 ± 15 mg of product solution, containing 117 μg of TAA. The first volunteer received 30 μCi of labeled TAA at time of administration, whereas the remaining volunteers received 174 ± 14 μCi.

The duration of data acquisition in the vertical position varied by volunteer according to the personal tolerance of each (first subject, 45 min; remaining three subjects, 55–65 min). Acquisition in the supine position then continued until 2 hr after administration. When the regional data were corrected for the scanning time that was lost during repositioning of the volunteers, smooth curves of the time course of the dose distribution in each region of interest were obtained.

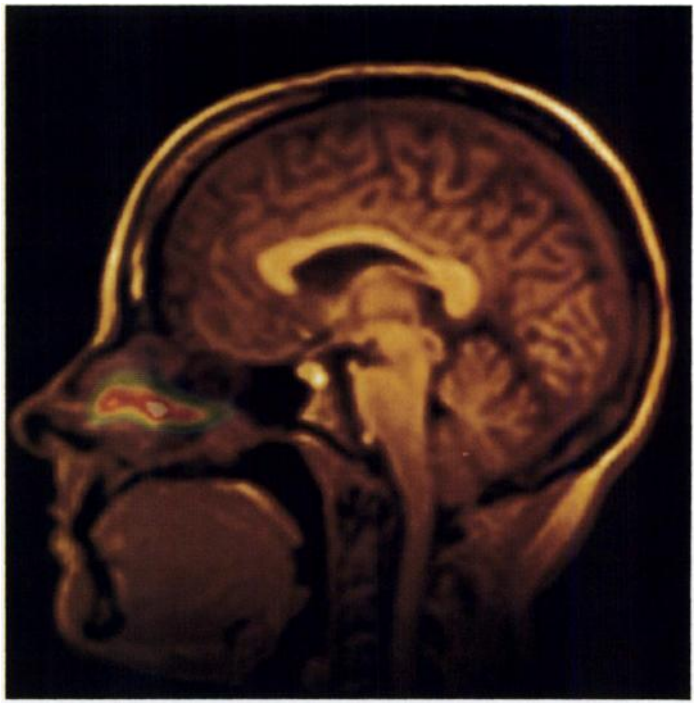

FIGURE 2. Display of PET data on MRI template, single sagittal slice through three-dimensional dataset, 8 mm from center plane of head. PET data are displayed with translucent rainbow color scale (blue as low counting rate to white as high counting rate), overlaid on MRI single-tone image.

The PET scans were displayed as a function of time after dosing and superimposed on the MRI scans. They showed that TAA in the product was delivered rapidly into the turbinates and frontal regions of the nose and into the sinuses. (Figs. 2 and 3) The distribution of TAA did not change rapidly in the first minutes after administration. During the first 30 min after dosing, some TAA was observed clearing into the throat and being swallowed in a fashion consistent with normal mucociliary clearance. Some may also have been absorbed through the tissues into systemic circulation. The majority of the dose initially distributed over the target tissues (frontal and maxillary sinuses, frontal cavity and all turbinate regions) and a slow clearance could be observed during the remainder of the study. A significant amount of drug was still observed in the target regions at the end of the study (Fig. 3). The maximum delivery of drug into all nasal target regions was observed within 3 min after dose administration. There was initially some variation between drug deposition in various regions, notably a difference between the left and right sides of the nose. Redistribution occurred over the first few minutes of the scan, resulting in more uniform dose distribution during the majority of the study. Average maximum uptake and ranges of maximum uptake in selected target regions are shown in Table 1, along with the uptake remaining in each region at various times after administration. At the end of the 2-hr observation period, the percentage of the administered dose that remained in each target region was reduced but remained measurable by PET.

DISCUSSION

Our initial concept for a study to examine the pharmacokinetics of an inhaled drug in the nasal passages called for volunteers to be scanned by PET in the traditional supine position. The approach fit the constraints imposed by the scanner but presented problems that would have to be addressed during the data interpretation. The drug formulation is an aqueous spray, presumably subject to gravitational runoff. The thixotropic formulation, developed to increase the stability of

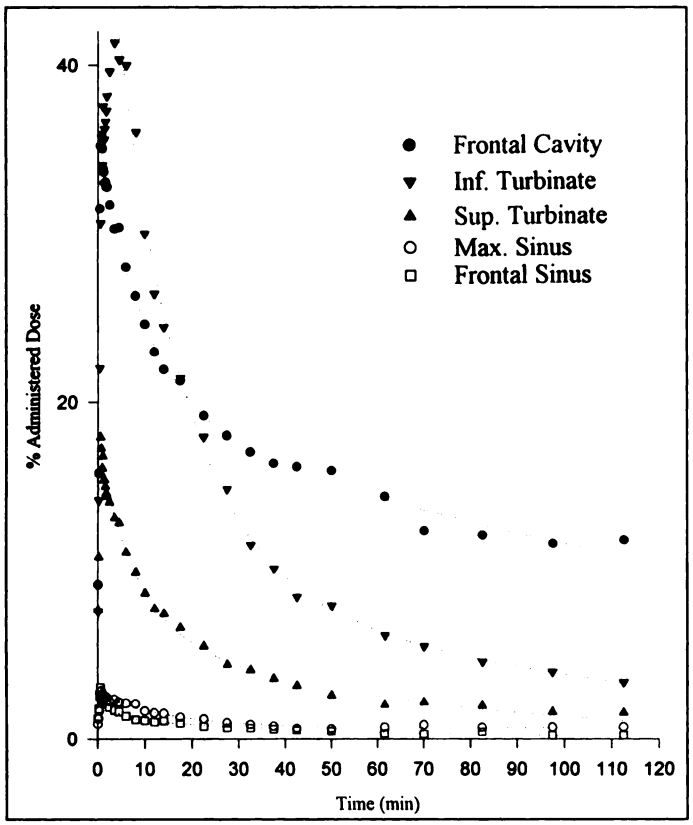

FIGURE 3. Uptake of Nasacort® AQ in target regions of interest. Symbols represent average of measured data from three volunteers and are placed at midpoint of each PET time frame. Dotted lines represent biexponential curves through data. Inf. = Inferior; Sup. = Superior; Max. = Maxillary.

TAA in the aqueous formulation, has a high viscosity, which was expected to minimize runoff from the target tissues of the nose. However, this study was partly designed to experimentally evaluate the effectiveness of that formulation in vivo. We could not assume that the drug distribution would be unaffected by the force of gravity. Differences in gravitational redistribution of the drug in the supine as opposed to the normal vertical position would have to be considered. The experimental design, therefore, called for several groups of volunteers to be scanned in the supine position with the scans beginning at different time intervals after administration of the dose. It remained possible that position-dependent differences in distribution of the dose would confuse the data interpretation of a multigroup study and require larger groups. Another solution to the problem was to perform the scan in the head-vertical orientation, which is normal for patients using the medication. This presented obvious technical problems in positioning and supporting the volunteers in the scanner. The support device that was designed for the study was intended to prolong the endurance of a volunteer in a semikneeling position without head motion. We hoped it would allow scanning in the vertical position for at least 20 min to ensure that the majority of any gravity-induced drug redistribution would occur normally. Water absorption, evaporation and runoff were expected to reduce the effect of gravity to negligible levels within several minutes after administration. In practice, the last three volunteers were able to tolerate the kneeling position for an average of 1 hr (55–65 min). This reduced the complexity and cost of the experiment and produced useful results after acquisition of only three full datasets.

PET images from the emission scans were not readily aligned with MRI images by direct manipulation. The radiopharmaceutical concentrated at the point of delivery in the nasal passages and, therefore, contained very limited reference information for superimposition of the two images. PET transmission scans were reconstructed and used for image registration. The emission scans were then subjected to the same spatial transformations as the corresponding transmission image. This procedure required that motion during the study be strictly limited. For this reason, regular checks of the position of the volunteer were made during the scan, and notes were kept regarding the direction and magnitude of any changes in position. After the adjustments made in response to the results of the first experiment were completed, position deviations were <3 mm throughout the study in any axis and generally <1 mm.

The study data show that the drug was distributed rapidly into the turbinate and sinus areas after administration. The frontal cavity and the turbinates (the majority of the divided passages through which air is filtered and humidified during passage through the nasal airway) are the most important target regions, and they become inflamed during allergic rhinitis. The data also show that the majority of the administered dose was retained in the target area, as opposed to being swallowed immediately after dosing. The sum of activity observed in all PET regions of interest during the first 6 min after administration was 92%–99% of the independently measured administered dose, of which 90%–95% represented drug in target areas (turbinates, sinuses and frontal cavity). Maxima in different regions occurred at different times. In all cases, a large portion of the dose was observed on the turbinates. Combined turbinate regions contained 50%–64% of the total dose. The largest portion of the administered dose was in the inferior turbinate region (40%–46%) in two volunteers, and in the third, the frontal cavity received somewhat more (55% compared to 42%). It is interesting to note that the amount of drug observed in the sinuses of the volunteers did not vary with the distribution of dose between the frontal cavity and the turbinates. Furthermore, the observed kinetics (Fig. 3) of the frontal region compared to the

TABLE 1
Data for Selected Regions of Interest (% of Administered Dose)

Region	Max	Postadministration				
		15 min	30 min	60 min	90 min	120 min
Frontal cavity	40, 55, 22	31, 33, 10	18, 29, 5	13, 26, 3	12, 21, 2	12, 21, 2
Inferior turbinate	46, 42, 41	25, 41, 25	10, 16, 15	4, 7, 7	3, 5, 5	3, 4, 4
Superior turbinate	19, 15, 24	13, 6, 10	3, 3, 7	1, 2, 3	1, 2, 2	1, 2, 1.5
Frontal sinus	4, 4, 3	1.5, 1, 1	0.5, 0.9, 0.7	0.1, 0.7, 0.2	0.03, 0.5, 0.1	0.08, 0.5, 0.1
Maxillary sinus	4, 2, 4	3, 1, 2	1, 0.5, 1	1, 0.5, 1	0.8, 0.3, 0.5	0.7, 0.9, 0.5

Measured data include the dose at the time of maximum uptake (Max) and the measured percentages of inhaled dose remaining in each region at several times postadministration in each volunteer. The order of the data in each case is Volunteer 2, 3 and 4, respectively.

turbinates and especially the inferior turbinates suggest that the drug was moving from the frontal cavity over the turbinates and then being cleared toward the throat. This would also be expected due to the normal mucociliary clearance mechanisms, which are known to not be affected by the drug. This motion, suggested by the data curves, was clearly visible in time-lapse video display of the data. The frontal cavity may be serving as a reservoir of drug to replenish that being eliminated from the turbinates. The superior turbinates received about half the total dose of the inferior turbinates and also exhibited more pronounced individual variation in curve shape during the first 10 min after inhalation. Those variations correlated (inversely) with changes in the frontal cavity uptake. Individual differences strongly diminished after the first 10 min. Other clear conclusions from the data are that the amount of drug in the target areas remains significant at 1.5 hr postadministration and that the clearance rates (Table 1) suggest that the drug will persist in those areas. This is an important observation in light of the fact that the target areas are well perfused, so a drug that was readily dissolved and absorbed into the tissues could be rapidly removed. The observation period was limited by the half-life of the ^{11}C label, so it is difficult to estimate and extrapolate the slow washout or absorption component of the curves. Still, simple linear or exponential extrapolations predict that microgram amounts of drug should be present on the target tissues for at least several additional hours.

CONCLUSION

The purpose of this study was limited to demonstration of the ability of PET to provide this unique type of information and to function effectively for measurement of dose delivery and pharmacokinetics. It was not intended to address clinical use and effectiveness or to assess the delivery system. It is clear that regional biodistribution and kinetic data for the active ingredient in the drug formulation could not be determined by other means. This direct in vivo evaluation of the formulation in only three volunteers is a more reliable indicator of its performance than inferences drawn even from extensive in vitro experiments. Despite the small sample size and expected intersubject variations, the study shows effective deposition of drug into the target tissues and demonstrates that the clearance of drug from the target areas is slow enough to allow significant amounts of drug to be present for at least several hours. This information was not otherwise available to the manufacturer of the formulation. Although penetration of drug into the sinus cavities was not expected, it has now been demonstrated and measured. We believe that this study clearly demonstrates the value and effectiveness of PET for investigation and screening of locally administered drug formulations.

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Increased Subglottic Gallium Uptake in Relapsing Polychondritis

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Gallium scintigraphy was performed on a 14-yr-old girl with subglottic airway narrowing that caused wheezing and dyspnea. The study showed increased gallium uptake in the neck. A biopsy was performed on the subglottic region, and the histology was compatible with relapsing polychondritis. After treatment with steroids, laboratory data that had indicated active inflammation soon normalized. Repeat gallium scintigraphy showed diminished uptake, although the subglottic stenosis did not improve. These results suggest that gallium scintigraphy is valuable for evaluating inflammatory activity in relapsing polychondritis.

Key Words: relapsing polychondritis; gallium scintigraphy; tracheal stenosis

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Relapsing polychondritis is thought to be a rare disorder characterized by inflammation of cartilaginous structures throughout the body. Its cause is unknown but it is thought to be autoimmune mediated. The inflammatory process commonly involves the ears, eyes and joints, resulting in pain and deformity. In more than 50% of patients, the cartilages of the upper airway are affected. In such patients, the stenotic lesions can be life threatening and tracheostomy may be required. We describe gallium scintigraphy in a patient with relapsing polychondritis presenting persistent wheezing and inspiratory dyspnea.

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