Evaluation of the Safety of Hyperpolarized Helium-3 Gas as an Inhaled Contrast Agent for MRI

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Introduction: Hyperpolarized He-3 gas is used as an inhaled contrast agent for MR imaging of the lungs. In the United States, the gas has not been approved for routine clinical use and imaging studies are only performed on an investigational basis. The purpose of this study was to assess the safety of inhaled hyperpolarized helium-3 gas as a contrast agent for MR imaging.

Methods and Materials: The electronic case report forms from all subjects who underwent hyperpolarized helium-3 MR imaging at the University of Virginia during the 7 year period from 6/1/99 to 5/30/06 were reviewed. Inhalation of the gas was approved by the United States Food and Drug Administration (FDA) as an Investigational New Drug (IND # 57,866) with requirement that the following safety tests be performed before and after each MR scan: vital signs (pulse, blood pressure, temperature, pulse oximetry), spirometry (FVC, FEV1, FEV1/FVC), blood work (complete blood count, standard chemistries, PT, PTT), and urine analysis. Helium dosing records were also evaluated. Subjects were checked for adverse events up to 24 hours after dosing. Adverse events were categorized by their likely relationship to the helium-3 inhalation as either related, possibly related, or not related, and whether the symptoms were mild (resolving spontaneously, requiring no treatment) or severe (requiring treatment). Adverse events were further categorized as *respiratory* if they involved symptoms of the respiratory tract (e.g. cough, chest tightness) and *non-respiratory* (e.g. stomach ache). The helium-3 scans associated with respiratory adverse events were compared with all other scans (non-respiratory and no adverse event) for demographic data, safety tests and helium-3 dosing parameters using a t-test, Mann-Whitney rank sum test, or Fisher exact test, as appropriate. A second similar analysis was performed for the group of scans associated with related and possibly related adverse events as compared with all other scans (unrelated and no adverse event). The data was also analyzed using the Bonferroni correction for multiple comparisons.

Results: 818 hyperpolarized helium-3 scans were performed in 528 different subjects (220 male, 308 female) age 4 to 80 years (mean 36±19 yrs). One to 10 helium-3 doses (mean, 3.7±1.7 doses/scan) with a volume of 50-1000 mL of helium-3 per dose were administered per MR scan with total of 3000 doses administered over the 7 year period. An adverse event was associated with 78 (9.5%) of the helium-3 MR scans with 61 (7.4%) considered related or possibly related to the helium-3 inhalation and 50 (6%) related to the respiratory system. The majority of the adverse events were mild, 76 (97%). Of the 2 severe adverse events, only one was thought to be related to the helium-3 inhalation, and this adverse event occurred in a 23 year old female who had atypical asthma characterized by severe, chronic cough. She had been hospitalized 3 times in the month preceding the helium MR scan for uncontrolled cough. In this subject two helium-3 doses were given, and the inhalation of the first dose was uneventful. However, after inhaling the second dose, the subject developed a severe uncontrolled cough that ultimately required treatment. The second severe adverse event occurred in a 5 year old male with bronchopulmonary dysplasia. Approximately 1 week after MR scan, he developed bronchospasm that required treatment, but it was felt by child's pulmonologist that the symptoms were likely related to his underlying disease and not to the helium-3 gas inhalation. Nonetheless, in compliance with regulatory requirements, this was reported as an adverse event.

Comparing the group with a respiratory adverse event to those without a respiratory adverse event, women were over-represented in the respiratory adverse event group (80% vs 62%, p=0.010). In addition, there was a trend toward more subjects with a respiratory disease in the respiratory adverse event group (74% vs 60%, p=0.052). The FVC (%pred) after helium-3 inhalation was slightly higher in the respiratory adverse event group (99±17% vs 93±19%, p=0.03), and a similar trend was present before the helium-3 inhalation (100±19% vs 94±20%, p=0.053). In the respiratory adverse event group, the baseline and post MR scan blood CO_2 were slightly lower (baseline 23±2.4 vs 24±2.6 mmol/L, p=0.009; post MRI 24±2.8 vs 24±2.5 mmol/L, p=0.019), and the baseline white blood cell count was slightly lower (6.1±2.1 vs 6.9±2.3 k/uL, p=0.038). There were no significant differences between the respiratory adverse event group and all other subjects for all other parameters (height, weight, BMI, smoking history, vital signs, blood laboratory, or spirometry). Comparing the related/possibly related adverse event group to all other subjects, women were over-represented in the adverse event group (79% vs 62%, p=0.0085), but subjects with a respiratory disease were not (66% vs 60%, p=0.50). In the adverse event group, the FVC (%pred) at baseline and after gas inhalation were slightly greater, the baseline serum potassium slightly lower, the baseline white blood cell count slightly lower, and the post inhalation serum CO_2 slightly higher. No other statistically significant differences were found. These differences did not remain statistically significant following the Bonferroni correction.

Evaluating the relationship between the helium-3 dosing parameters and adverse events, the total volume of helium-3 administered was higher in the respiratory adverse event group (1352±439 mL vs 1145±512 mL, p=0.0055) and in the related/possibly related adverse event group (1284±445 mL vs 1148±514 mL, p=0.046). No other helium-3 dosing parameters were significantly different in the adverse event groups including the number of doses administered and the total volume of helium-3 plus diluting gas inhaled.

Discussion: In our study, it was found that the inhalation of hyperpolarized helium-3 gas is safe with adverse events occurring in a relatively small (11%) number of cases with respiratory adverse events occurring in only 6% of subjects. In the vast majority, the adverse events were mild with the symptoms resolving spontaneously. Women were more likely to report adverse events than men, and respiratory adverse events were more likely in subjects with an underlying lung disease. No clinically significant differences in the FDA required safety tests were found in the group of subjects with respiratory adverse events, or the group of subjects with adverse events that were related or possibly related to the helium-3 inhalation. The only helium-3 dosing parameter associated with adverse events was the total volume of helium-3 administered. Thus, hyperpolarized helium-3 is a well tolerated contrast agent.

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