Factors affecting accuracy of carbon monoxide diffusing capacity devices used in clinical trials for inhaled insulin

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Abstract

Introduction: Measurements of carbon monoxide diffusing capacity (DLCO) are a primary safety outcome for MannKind Corporation’s clinical trials of inhaled insulin powder (Technosphere® Insulin). Accuracy of DLCO devices is difficult to assess even with biological controls.

Methods: A protocol to control for accuracy of the measurements required use of a simulator for DLCO (Hans Rudolph, Kansas City, MO) that mimics patient tests and creates exact known DLCO values. Laboratories measuring DLCO for clinical studies tested their device every 8 weeks. At each of 3 inspired volumes and 2 simulated gas levels, 4 to 5 sequential simulations were performed. Data recorded from the DLCO device were compared to the “target” values generated by the simulator. Each laboratory was required to first demonstrate that their equipment met the study protocol accuracy requirement which required that DLCO, VA, and IVC be within 10% of target values. Each PFL completed 5 sequential simulated DLCO tests were performed. Data recorded from the DLCO device were compared to the “target” values generated by the simulator. Devices were considered in control if within ±10% of target (% Difference). We examined six factors that might have been associated with the degree of error and failing to be within control: 1) Device Type, 2) Inspired Volume (VI), 3) Alveolar Volume (VA), 4) System Dead Space volume, 5) Tracer gas type, and 6) Temperature.

Results: 16,369 DLCO simulations were performed. Systems outside of control limits were detected on 948 (5.8%) tests and corrective actions taken to bring the systems into control (see Figure 3). Average % Diff ranged from −5.0 to +2.1% between devices with different devices being significantly different from one another, P<0.01 (see Figure 4).

Quality Control of PF Labs

Figure 1: DLCO simulator.

Figure 2: EasyLab QCTM testing information screen shot.

Figure 3: Percent difference in DLCO between target and measured.

Figure 4: Equipment performance.

Figure 5: DLCO accuracy and variance related to room temperature.

Figure 6: Performance by Deadspace Volume (ml).

Figure 7: Performance by inspired volume of test gas.

Figure 8: Relation between mean % Difference in DLCO and measured VA.

Conclusion: Several factors affect DLCO instrument performance. Testing DLCO instruments used in clinical trials is necessary to identify instruments falling accuracy criteria that could affect outcomes.

Conclusions: Testing DLCO instruments used in clinical trials is necessary to ensure test accuracy due to the many factors that may alter outcomes.