A Novel Approach to Administer Treprostinil to Intubated Patients Using a Vibrating Mesh Nebulizer

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Rationale: There has been much interest in the use of prostanoioids in the treatment of pulmonary hypertension in adult ventilated patients. Administration of epoprostenol (Flolan\textsuperscript{\textregistered}) via continuous nebulization has had some success, but that drug has not yet received approval for inhalation from the U.S. Food and Drug Administration. However, several other prostanoioids have already qualified for use via inhalation to ambulatory patients using specific nebulizers. These nebulizers cannot be easily adapted for use during mechanical ventilation, resulting in the discontinuation of therapy when the patient falls critically ill. Tyvaso\textsuperscript{\textregistered} (formulation of inhaled treprostinil, United Therapeutics Corp., Silver Spring, MD) represents one such drug. For ambulatory patients, Tyvaso is administered four times daily via a proprietary "pulsed" ultrasonic nebulizer system (the TD-100\textsuperscript{\textregistered}, United Therapeutics, see the Tyvaso website), which includes hyperlinked information pertaining to the TD-100. Dosing is based on intermittent doses given at 1- to 4-hour intervals over 3 to 9 breaths. Our hypothesis was that, combining inhaled dose data on ambulatory delivery with knowledge of in vitro performance of a nebulizer used with the ventilator, we could propose dosing strategy for an intubated adult patient.

Methods: One 2.9 mL ampule of Tyvaso aqueous solution contains 1.74 mg of treprostinil (0.6 mg/mL) which is used for four treatments administered during one day of therapy. The manufacturer recommends that the patient initially inhale three breaths and gradually increase to no more than nine breaths. Assuming a residual drug volume ("dead volume" of the TD-100) of 1.0 mL, 1.5 mL of drug would be available for inhalation to the ambulatory patient. This equates to a maximum of 0.435 mL (0.285 mg) for each of the four standard doses. Using published data of particle size distribution, we estimated lung dose based on respirable fraction of inhaled dose. Combining this with previously published data on aerosol delivery efficiency of type and position of the vibrating mesh nebulizer (VMN; Solo, Aerogen, Galway, Ireland) placed immediately after the humidifier on the inspiratory limb of the ventilator circuit, we established a range of nominal dose between 0.25 and 0.75 mL, in 0.25-mL aliquots. Because of the 90- to 120-minute half-life of the drug, we decided to repeat incremental 0.25-mL doses at 15-minute intervals until the desired effects were observed.

Results: Upon administration of the initial 0.25 mL of treprostinil via the VMN, no positive or deleterious effects were observed. After 15 minutes, another 0.25 mL of solution was nebulized to the patient via the VMN. With the second incremental dose, the mean pulmonary artery pressure fell from 40 mm Hg to 36 mm Hg with no sign of reduced systemic blood pressure, and the arterial oxygen saturation (SpO\textsubscript{2}) increased from 91% to 96%. No adverse response was observed during or after administration.

Conclusions: Based on the use of in vitro data, we were able to propose a strategy for administration of treprostinil (Tyvaso) to a ventilated adult patient. Dosing will vary based on the ventilator settings, nebulizer type, and position of the nebulizer in the circuit. Further studies are required to establish safe and effective dosing during mechanical ventilation of aerosolized prostanoioids approved for inhalation to ambulatory patients.

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