Relative bioavailability of terbutaline to the lungs following inhalation using different methods

Abstract

Keys words: terbutaline, urine, MMAD, FPD, relative lung bioavailability, Turbuhaler, spacers, nebulisers.

The primary aim was to validate and implement a urinary pharmacokinetic method for terbutaline to determine the relative lung and systemic bioavailability following inhalation and to measure the in-vitro characteristics of the emitted dose by these inhalation methods.

Two new robust, accurate and sensitive high performance liquid chromatography methods for the determination of terbutaline in aqueous and urine samples were validated in accordance with the FDA and ICH guidelines. Terbutaline was extracted using solid phase extraction with salbutamol and bamethane as internal standards. The accuracy, precision, lower limit of detection and recovery for both methods were within recognized limits.

The in-vitro characteristics of terbutaline sulphate inhalers were measured according to standard compendial methodology as well as adaptation of this methodology to simulate routine patient use. The dose emission of terbutaline sulphate from a Bricanyl Turbuhaler was determined using an inhalation volume of 4 L at inhalation flows of 10-60 L min^{-1}. The particle size distribution was measured using an Anderson Cascade Impactor (ACI) with a mixing inlet valve to allow measurement at different flows. A steady increase in total emitted dose (TED) and the fine particle dose (FPD) was observed as the inhalation flow increased thereby highlighting the flow dependent dose emission characteristics of the Turbuhaler.

The in-vitro dose emission characteristics of terbutaline sulphate from Bricanyl MDIs were measured according to the standard compendial methodology at a flow of 28.3 L min^{-1} using a 4 L inhalation volume. The TED and particle size distribution of terbutaline sulphate from the Bricanyl MDI were determined alone and with different spacers [AeroChamber Max (AMAX), AeroChamber Plus (APLUS), Fisonair and Nebuhaler]. The TED from the MDI alone was significantly higher than all MDI+spacers ($p<0.001$). The MDI with APLUS resulted in the smallest mass median aerodynamic diameter (MMAD) and the highest fine particle fraction (FPF). The MDI with AMAX resulted in the highest FPD.

The in-vitro characteristics of terbutaline sulphate from Bricanyl respules using the Aeroneb Pro (vibrating mesh) and Sidestream jet nebulisers were determined by the CEN methodology and the Next Generation Impactor (NGI) methodology. The Aeroneb Pro was found to have significantly better aerodynamic properties than the Sidestream. The results from the NGI method were significantly different from the CEN method suggesting further evaluation of both methods. Cooling the NGI decreased the evaporation effect.

Twelve healthy volunteers (6 females) completed in-vivo urinary terbutaline pharmacokinetic studies to determine the relative bioavailability following inhalation. The differences between the amounts excreted 0.5, 1, 2, 4, 6 and 24 hour post inhalation from a Bricanyl MDI (I) and oral (O) dosing of 500 µg terbutaline sulphate and with the co-administration of oral charcoal (IC and OC, respectively) were studied. No terbutaline was found in OC samples. The amount of terbutaline excreted 30 minutes post I and IC were significantly ($p<0.001$) higher than post O suggesting that the amount of terbutaline excreted 30 minutes post dosing can be used as an index of the lung deposition. The amount of terbutaline excreted 24 hour post I was significantly ($p<0.01$) higher than post O suggesting that the amount of terbutaline excreted 24 hour post dosing can be used as an index of the relative systemic bioavailability. The dose response relationships and the low inter and intra-subject variability studies confirm the feasibility of this method.

To demonstrate the application of the method the effect of inhalation technique on the lung and systemic bioavailability following inhalation from a dry powder inhaler was evaluated. The effect of different spacers on the dose emitted from the Bricanyl MDI and the effect of different nebulisers on the dose emitted were also studied using twelve healthy volunteers (6 females) for each study.

A fast inhalation flow using the Bricanyl Turbuhaler resulted in significantly higher amounts of terbutaline excreted 0.5 and 24 hour post dosing (2 doses of 500µg terbutaline sulphate from Bricanyl Turbuhaler) than slow inhalation flow ($p<0.001$). The Bricanyl MDI alone resulted in a significantly higher amount of terbutaline excreted 24 hour post dosing (2 doses of 250µg terbutaline sulphate from Bricanyl MDI) and significantly lower amounts excreted 30 minutes post dosing than the MDI+Spacers. The AMAX provided a greater amount of urinary terbutaline excreted 30 minutes post dosing than the APLUS and Nebuhaler. The Aeroneb Pro resulted in significantly higher amounts of terbutaline excreted 0.5 and 24 hour post dosing (1 dose of 5mg/2ml terbutaline sulphate from Bricanyl respule) than a Sidestream Jet nebuliser ($p<0.001$).

Further application of the method was demonstrated by 12 (6 female) COPD non-invasive mechanically ventilated patients. One dose of 2mg in 0.8ml terbutaline sulphate respiratory solution from Aeroneb Pro and one dose of 5mg in 2ml terbutaline sulphate respiratory solution from Sidestream jet nebuliser resulted in a similar amounts of urinary terbutaline excreted 0.5 and 24 hour post dosing. The results were consistent with the results of the ex-vivo study performed on the same patients.

The thesis highlights extension of the urinary pharmacokinetic method following inhalation to terbutaline and its application in volunteer and patient studies.