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'Martindale the complete drug reference,' PHARMACEUTICAL PRESS,(1999) 32nd Edition, pp. 1034-1035.
Chinese Journal of Experimental & Clinical Virology, June 2007, vol. 21, no. 2, pp. 132-134
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(54) Title: METHODS FOR ADMINISTERING CORTICOSTEROID FORMULATIONS

(57) Abstract: Described here are methods for the treatment of respiratory conditions using nebulized corticosteroids. The methods administer a dose of corticosteroid twice a day or more with nebulization times of 5 minutes or less. The faster nebulization times improve patient compliance. The methods also employ a lower corticosteroid dose while achieving therapeutic efficacy similar to commercially available formulations. This results in improved patient safety by reducing the systemic exposure of the corticosteroid.

METHODS FOR ADMINISTERING CORTICOSTEROID FORMULATIONS

Field of the Invention

The methods described here are in the field of respiratory medicine. Specifically, methods that administer corticosteroid formulations by nebulisation are described. More specifically, methods for the treatment of asthma that administer lower doses of corticosteroid, and which are associated with improved patient compliance and safety are described.

Background of the Invention

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

Asthma is a pulmonary condition characterised by airway inflammation, airway hyperresponsiveness, and reversible airway obstruction. During asthmatic episodes, afflicted individuals often experience labored breathing, wheezing, and coughing. These symptoms may be treated with medications such as corticosteroids, which are administered via pressurized metered-dose inhalers (pMDIs) or dry powder inhalers (DPIs). However, certain patient populations, e.g., pediatric, neurologically impaired, or elderly asthmatics, may lack the breath coordination needed for pMDIs or lack the lung capacity needed to use DPIs. Thus, these asthma patients require the administration of therapy via nebulizers.

Formulations that undergo nebulisation are dispersed in air to form an aerosol of very fine liquid droplets suitable for inhalation into the lung. Nebulizers typically use compressed air, piezoelectric or servomechanically generated ultrasonic waves, or a vibrating mesh to create the mist of the droplets, and may also have a baffle to remove larger droplets from the mist by impaction. A variety of nebulizers are available for this purpose, such as soft mist nebulizers, vibrating mesh nebulizers, ultrasonic nebulizers, jet nebulizers, and breath-actuated nebulizers. In use, the nebulized formulation is administered to the individual via a mouthpiece or mask.

Low patient compliance is a generally known problem with nebulized drugs. This is primarily due to the amount of time required for nebulizing the drug, which

can last up to 30 minutes or longer, depending on such factors as the volume of liquid formulation to be nebulized, the particular active agent being nebulized, the concentration and surface tension of the active agent in the formulation, and the resulting viscosity of the formulation. Other factors include the condition or symptom being treated, and whether the active agent is present as a solution or suspension. Active agent formulations are generally supplied as nominal 2.0 ml volumes with solution or suspension viscosities ranging from that of water, to 100 times the viscosity of water. These typically require about four to about 20 minutes to nebulize, with the nebulisation time increasing as the viscosity increases from that of water. If the formulation is a suspension, an additional 15% to 30% longer time is required to nebulize than solution formulations with comparable viscosities due to the added energy required to from droplets containing suspended particulates. Children and adults who become impatient because of lengthy nebulisation times often stop treatment prematurely. Drug delivery is often not linear over time, with the bulk of the drug being delivered near the end of the recommended nebulisation time. Thus, early termination of treatment can result in a disproportionally decreased delivery of drug. This can lead to further non-compliance since the inadequate dose will likely fail to provide adequate therapy, and thus discourage further use of the nebulizer treatment regimen.

Another issue with nebulizing drugs relates to the amount of drug actually delivered to the lungs. For example, when nebulizing budesonide using a conventional jet nebulizer, the doses of budesonide are those added to the nebulizing device. However, only approximately 40% to 60% of the drug typically leaves the nebulizer, so only approximately 40% to 60% of the nominal dose is delivered to the patient. This is because the drug is delivered constantly, and when the patient is exhaling, the drug leaving the nebulizer will not be delivered to the patient; instead, it will be lost to the environment. Of the amount delivered to the patient, only a fraction is in droplets having diameters in the respirable range (less than approximately 5 microns) which leaves approximately 10% to 20% of the nominal dose delivered to the lungs. To increase the amount of budesonide delivered to the lungs, either the budesonide dose volume or concentration can be increased. In turn,

this may lead to higher maximum plasma concentrations, which are associated with a greater risk of systemic side-effects such as cortisol suppression.

It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

Consequently, new methods for administering nebulized drugs would be useful that maximize compliance and therapeutic efficacy while minimizing safety issues or side effects. Specifically, administration methods having faster nebulisation times would be desirable to improve patient compliance. Administration methods that result in improved lung deposition (marker of enhanced therapeutic efficacy) without increasing systemic or oropharyngeal exposure (which leads to side effects) would also be desirable.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

Although the invention will be described with reference to specific examples it will be appreciated by those skilled in the art that the invention may be embodied in many other forms.

Summary of the Invention

According to a first aspect of the present invention there is provided a method for treating a respiratory condition comprising administering a dose of about 0.30 mg or less of a corticosteroid at least twice a day, wherein administration of the corticosteroid dose results in a pharmacokinetic profile characterised by a T_{max} that is less than about 5 minutes and an $AUC_{0\text{-}inf}$ that does not exceed about 60,000 pg-min/mL when administered for at least 7 days.

According to a second aspect of the present invention there is provided a method for treating a respiratory condition comprising administering a dose of about 0.30 mg or less of budesonide at least twice a day, wherein administration of the budesonide dose results in a pharmacokinetic profile characterised by a T_{max} that is less than about 5 minutes, a C_{max} less than about 850 pg/mL, and an $AUC_{0\text{-}inf}$ that

does not exceed 60,000 pg-min/mL when administered repeatedly for at least 7 days.

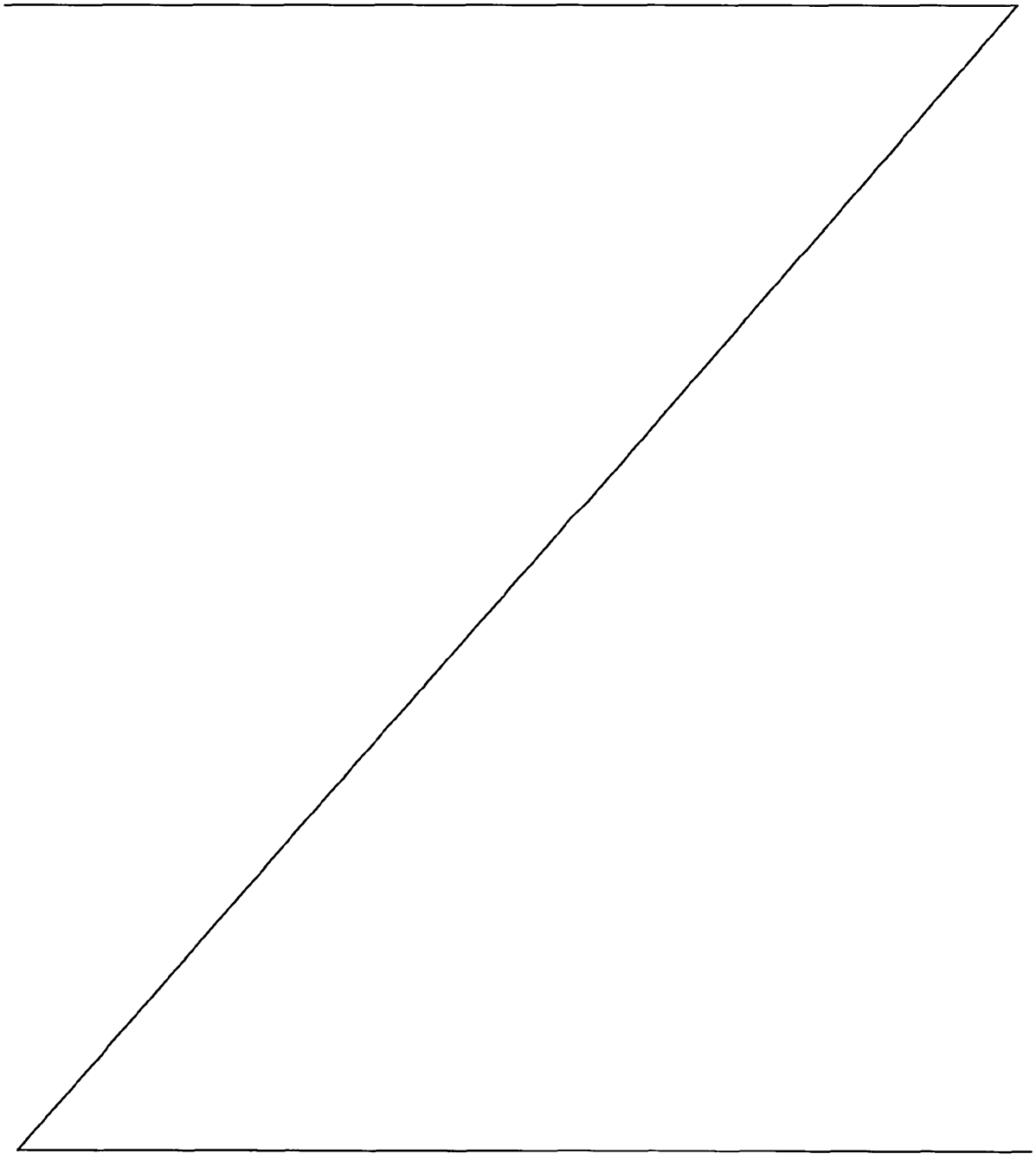
According to a third aspect of the present invention there is provided a method for treating a respiratory condition comprising administering a dose of 0.30 mg or less of a corticosteroid by nebulisation twice a day for at least a six week period to a patient afflicted with the respiratory condition, wherein the $AUC_{0\text{-}inf}$ of the administered corticosteroid does not exceed about 60,000 pg-min/mL during the six week period, and the T_{max} is less than about 5 minutes.

According to a fourth aspect of the present invention there is provided a method for reducing one or more systemic side-effects of corticosteroids comprising administering a dose of about 0.30 mg or less of a corticosteroid twice a day for at least six weeks in an aerosol, wherein the $AUC_{0\text{-}inf}$ is less than about 60,000 pg-min/mL, and the T_{max} is less than about 5 minutes.

Described here are methods for the treatment of respiratory conditions using nebulized corticosteroids. The methods may include administration of a dose of corticosteroid at least once a day with nebulisation times that are faster than commercially available formulations. This administration regimen improves patient convenience by minimizing delivery times as evidenced by time to maximum plasma concentrations, and thus, may improve patient compliance. Further, because of the unexpected pharmacokinetics exhibited by the administered corticosteroid, as further detailed below, a lower dose of the corticosteroid may be used in comparison to commercially available formulations while achieving similar lung dose and therefore therapeutic efficacy. For example, low doses of 0.25 mg or 0.125 mg or less of budesonide, a corticosteroid, may be administered. This results in improved patient safety by reducing the systemic exposure of the corticosteroid.

In one variation, the methods for treating respiratory conditions include administering a dose of a corticosteroid once a day by nebulisation for at least one week (7 days), at least two weeks (14 days), at least three weeks (21 days), at least four weeks (28 days), at least five weeks (35 days), or at least six weeks (42 days) or more. For example, the corticosteroid may be administered for at least two months or at least three months or more if required. The corticosteroid may also be administered more frequently, for example, two, three or four times a day.

The methods also include nebulisation times that are faster than commercially available corticosteroid formulations. In one variation, the nebulisation time is about 5.0 minutes or less. In another variation, the nebulisation time is about 4.0 minutes of less. In yet another variation, the nebulisation time is about 3.0 minutes or less. In some instances, the nebulisation time may be less than about 2.0 minutes.



[0011] In one variation, the methods include administering a dose of about 0.30 mg or less of a corticosteroid at least twice a day, wherein the dose is administered by nebulization of a corticosteroid formulation and results in a pharmacokinetic profile characterized by a T_{max} that is less than about 5 minutes and an $AUC_{0\text{-}inf}$ that is 1.5 times the $AUC_{0\text{-}inf}$ of the initial dose, or increases by more than 1.5 times the $AUC_{0\text{-}inf}$ of the initial dose, when administered for at least 7 days. Here the pharmacokinetic profile may be further characterized by a C_{max} to $AUC_{0\text{-}inf}$ ratio that remains approximately constant over a predefined time period, a C_{max} that is less than about 850 pg/ml, an $AUC_{0\text{-}inf}$ that does not exceed 75,000 pg-min/ml, or a combination thereof. As used herein, the term "C_{max}" is defined as the maximum plasma concentration following administration, and "T_{max}" is defined as the time to maximum plasma concentration. By "AUC," it is typically meant "$AUC_{0\text{-}inf}$," which is the total area under the plasma drug concentration-time curve from time zero and calculated to infinity. Here the C_{max}, T_{max}, and AUC values are generally measured in units of pg/ml, minutes, and pg-min/ml, respectively.

[0012] In some variations, the methods for treating respiratory conditions comprise administering a dose of about 0.30 mg or less of budesonide at least twice a day, wherein administration of the budesonide dose results in a pharmacokinetic profile characterized by a T_{max} that is less than about 5 minutes, a C_{max} less than about 850 pg/ml, and an $AUC_{0\text{-}inf}$ that increases by more than about 1.5 times the $AUC_{0\text{-}inf}$ of the initial dose, but does not exceed 75,000 pg-min/ml when administered repeatedly for at least 7 days.

[0013] In another variation, for example when a dose of less than about 0.30 mg of a corticosteroid is administered twice a day for at least six weeks, the AUC (representative of the total amount of drug in the blood after a dose) of the administered corticosteroid at least doubles over the six week period. In one variation, the AUC does not exceed about 60,000 pg-min/ml when the AUC at least doubles. In yet another variation, the AUC does not exceed about 40,000 pg-min/ml when the AUC at least doubles. In further variations, the same corticosteroid dose will result in an AUC that triples over a six week period of therapy. However, these increased AUC values are generally less than or equivalent to a commercially available corticosteroid formulation for nebulization, as further elucidated below, whose profile is known to be safe and free of side effects. The methods may also result in an increase in C_{max} (maximum plasma concentration following administration) values. Despite the increase in maximum plasma concentrations, the administration methods may provide C_{max} to AUC ratios that are

approximately constant over predefined time periods. This tends to indicate that over repeated treatments, an increase in topical surface area is being treated, while keeping systemic exposure to a minimum.

[0014] The methods described here may also reduce one or more systemic side-effects of corticosteroids. In one variation, the methods include administering less than about 0.30 mg dose of a corticosteroid twice a day for at least six weeks in an aerosol, wherein the C_{max} is less than about 850 pg/ml.

[0015] Methods for reducing one or more systemic side-effects of corticosteroids comprising administering a dose of about 0.30 mg or less of a corticosteroid twice a day for at least six weeks in an aerosol, wherein the $AUC_{0\text{-}inf}$ is less than about 75,000 pg-min/ml are also described.

[0016] The dose of corticosteroid that may be administered ranges from about 0.05 mg to about 1.0 mg. In some variations, the dose of corticosteroid is less than about 0.30 mg. In one instance, the dose is about 0.25 mg or less of corticosteroid. In another instance, the dose is about 0.135 mg or less of corticosteroid. An exemplary corticosteroid is budesonide, including derivatives, analogues, and salts thereof. The corticosteroid may be provided in a formulation that also includes surface active agents, stabilizers, buffers and other excipients.

[0017] The methods described here may be used to treat patients with various respiratory conditions. As used herein, the terms "treatment or treating" refer to the amelioration, reduction, or prevention of symptoms indicative of a respiratory condition. For example, the methods may be used to treat inflammatory airway conditions such as asthma, chronic obstructive pulmonary disease (COPD), Respiratory Distress Syndrome, chronic cough, and bronchiolitis. Infectious and neoplastic airway conditions are also contemplated. The patients that may be treated can be of any age, ranging from neonates, infants, children, and adolescents (pediatric age groups). The methods may also be useful in adults.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1 is a graphical representation of the mean plasma budesonide concentration-time profile obtained with nebulization of the 0.25 mg/1.5 ml budesonide formulation shown in Table 6.

[0019] FIG. 2 is a graphical representation of the mean maximum plasma concentration obtained with a dose of 0.25 mg budesonide provided by the formulation shown in Table 6 after the first administered dose and after six weeks of treatment (day 42).

[0020] FIG. 3 is a graphical representation of the mean plasma budesonide concentration-time profile obtained with nebulization of the 0.135 mg/1.5 ml budesonide formulation shown in Table 6.

[0021] FIG. 4 is a graphical representation of the mean maximum plasma concentration obtained with a dose of 0.135 mg budesonide provided by the formulation shown in Table 6 after the first administered dose and after six weeks of treatment (day 42).

DETAILED DESCRIPTION

[0022] Described here are methods for the treatment of respiratory conditions using nebulized corticosteroids. The methods administer a dose of corticosteroid at least once a day with nebulization times that are faster than commercially available formulations. For example, the nebulization times may be about 5.0 minutes of less, about 4.0 minutes or less, about 3.0 minutes or less, or about 2.0 minutes or less. This administration regimen improves patient convenience, and thus, may improve patient compliance. Further, because of the unexpected pharmacokinetics exhibited by the administered corticosteroid, as further described below, a lower dose of the corticosteroid may be used in comparison to commercially available formulations while achieving similar therapeutic efficacy. This results in improved patient safety by reducing the systemic exposure of the corticosteroid.

[0023] The methods described herein administer a corticosteroid at least once a day. However, corticosteroid administration may be repeated or administered more frequently. For example, the corticosteroid may be administered at least two times, at least three times, or at least four times a day. Scheduling may also be varied. For example, the corticosteroid may be administered twice a day for at least one week (7 days), twice a day for at least about two weeks (14 days), twice a day for at least three weeks (21 days), twice a day for at least four weeks (28 days), twice a day for at least 5 weeks (35 days), or twice a day for at least six weeks (42 days)

or more. In some variations, the corticosteroid is delivered twice a day every two days, twice a day every three days, twice a day every four days, twice a day every week, twice a day every two weeks, or twice a day every four weeks or more. These regimens may be continued as long as required.

[0024] The dose of corticosteroid may also vary, but will generally be a low dose. For example, when budesonide is used, the dose of budesonide that is administered may be less than about 0.30 mg. In one variation, the budesonide dose is between about 0.22 mg to about 0.27 mg. In another variation, the budesonide dose is between about 0.10 mg to about 0.27 mg. In other variations, the dose of budesonide administered is about 0.25 mg or less. In further variations, the dose of budesonide administered is about 0.135 mg or less. In some variations, a nebulizer may be used to generate the aerosol of corticosteroid for administration. Examples of commercially available nebulizers include the AERONEB™ and AERONEB GO™ nebulizers (Aerogen, San Francisco, CA); PARI nebulizers, including the PARI LC PLUS™, PARI BOY™ N, PARI eflow, PARI LC SINUS, PARI SINUSTAR™, PARI SINUNEB, and PARI DURANEB™ nebulizers (PARI Respiratory Equipment, Inc., Monterey, CA); MICROAIR™ nebulizer (Omron Healthcare, Inc, Vernon Hills, IL); HALOLITE™ nebulizer (Profile Therapeutics Inc., Boston, Mass.); RESPIMAT™ nebulizer (Boehringer Ingelheim Ingelheim, Germany); ERODOSE™ nebulizer (Aerogen, Inc., Mountain View, CA); OMRON ELITE™ (Omron Healthcare, Inc., Vernon Hills, IL); OMRON MICROAIR™ (Omron Healthcare, Inc, Vernon Hills, IL.); MABISMIST™ II nebulizer (Mabis Healthcare, Inc, Lake Forest, IL); LUMISCOPE™ 6610 nebulizer; (The Lumiscope Company, Inc., East Brunswick, NJ); AIRSEP MYSTIQUE™ nebulizer, (AirSep Corporation, Buffalo, NY); ACORN-1 and ACORN-11 (Vital Signs, Inc, Totowa, NJ); AQUATOWER™ nebulizer (Medical Industries America, Adel, IA); AVA-NEB (Hudson Respiratory Care Incorporated, Temecula, CA); AEROCURRENT™ nebulizer utilizing the AEROCELL™ disposable cartridge (AerovectRx Corporation, Atlanta, GA); CIRRUS (Intersurgical Incorporated, Liverpool, NY); DART (Professional Medical Products, Greenwood, SC); DEVILBISS™ PULMO AIDE (DeVilbiss Corp; Somerset, PA); DOWNDRAFT™ (Marquest, Englewood, CO); FAN JET (Marquest, Englewood, CO); MB-5 (Mefar, Bovezzo, Italy); MISTY NEB™ (Baxter, Valencia, CA); SALTER 8900 (Salter Labs, Arvin, CA); SIDESTREAM™ (Medic-Aid, Sussex, UK); UPDRAFT-II™ (Hudson Respiratory Care; Temecula, CA); WHISPER JET™ (Marquest Medical Products, Englewood, CO); AIOLOS™(Aiolos Medicnnsk Teknik, Karlstad, Sweden); INSPIRON™ (Intertech Resources,

Inc., Bannockburn, IL); OPTIMIST™ (Unomedical Inc., McAllen, TX); PRODOMO™ and SPIRA™ (Respiratory Care Center, Hameenlinna, Finland); AERx™, Essence™, and Ultra™ nebulizers (Aradigm Corporation, Hayward, CA); SONIK™ LDI Nebulizer (Evit Labs, Sacramento, CA); and SWIRLER® Radioaerosol System (AMICI, Inc., Spring City, PA). Exemplary vibrating membrane, mesh or plate nebulizers are described by R. Dhand (Respiratory Care, (December 2002), 47(12), p. 1406-1418).

[0025] The respiratory conditions that may be treated with the methods described here include without limitation, asthma, chronic obstructive pulmonary disease (COPD), emphysema, bronchitis, bronchiolitis, pneumonia, neoplasms of the large and small airways, and respiratory distress syndrome. The patients that may be treated can be of any age, ranging from neonates, infants, children, and adolescents (pediatric age groups). The methods may also be useful in adults.

[0026] The methods described here can provide more desirable pharmacokinetic parameters than commercially available corticosteroid formulations. An exemplary commercial formulation is Pulmicort Respules® ampules, referred to herein as "Pulmicort Respules." Pulmicort Respules are manufactured and sold as a budesonide inhalation suspension by Astrazeneca (Wilmington, DE), and supplied in doses of 0.25 mg, 0.50 mg, and 1.0 mg per 2.0 ml ampules. Presently, Pulmicort Respules are the only FDA approved nebulized corticosteroid product on the U.S. market for the treatment of pediatric asthma. Regardless of the dose, Pulmicort Respules are administered once daily.

Exemplary Method Of Treating Respiratory Conditions

[0027] In one variation of the method, desirable pharmacokinetic parameters were demonstrated in a randomized, double blind, placebo-controlled, six week study, in which efficacy, safety, and pharmacokinetics of the unit dose budesonide formulations (UDB) shown in Table 6 were assessed in 205 patients aged 4 to 18 years old with asthma. The budesonide was administered twice a day by a nebulizer for six weeks (42 days). In one subset, budesonide was administered at a dose of 0.25 mg. In the other subset, budesonide was administered at a dose of 0.135 mg. Treatment at either dose resulted in improvement of asthma symptoms. Additionally, faster nebulization times were observed as shown in Table 1, with average times of about 4.7 minutes at the beginning of treatment and decreasing to about 3.8 minutes at week six of

treatment. Nebulization times for comparable commercial formulations such as Pulmicort Respules are about 8 minutes or more in comparable subjects, as shown in Table 2.

Table 1. Mean Nebulization Time in Children Ages 2-18 Using PARI LC Plus Nebulizer

Mean time to sputter (mins)	Placebo	UDB 0.135mg	UDB 0.25mg
Visit 2	4.2	4.7	4.7
Visit 3	3.8	4.1	4.0
Visit 4	3.5	3.7	4.2
Visit 5	3.7	3.6	3.9

*Table 2. Pulmicort Respules Nebulization Time in Various Commercial Nebulizers For Administration to Children**

Nebulizer System	Type	Inhalation Time (min)	Dose Delivered (% of Nominal)	Diameter of Droplets (μm)
Omron NE -U22	Mesh	15	29 +/-1.4	5.6 +/-0.24
Omron NE -C16	Jet	9~12	10 +/-0.7	6.9 +/-0.16
Pari LC Plus	Jet	9	20 +/-1.0	6.2 +/-.031
Pari LC Plus Junior	Jet	9	18 +/-0.2	7.6 +/-0.26
Mefat 2000 (	Jet	12	9 +/-1.5	7.8 +/-0.70
Azwell Nescojet AZ-11	Jet	9	10 +/-1.7	7.7 +/-0.49
Nissho Inhaling Compressor	Jet	12	15 +/-2.2	9.9 +/-2.33
DeVilbiss PulmoAide 5650	Jet	9	11 +/-2.1	6.5 +/-0.41
Millicon-S	Jet	12	15 +/-1.4	7.4 +/-0.04
SideStream	Jet	8	4 +/-0.6	5.3 +/-0.11

* data translated for Japanese Ministry of Health Approval of Pulmicort Respules

[0028] The faster nebulization times shown in Table 1 resulted in shorter T_{maxs} (time to maximum concentration of drug in the blood after a dose). T_{maxs} averaged about 4.3 minutes (SD ± 0.63 minutes) for the two dosage strengths and time of treatment that ranged from zero to six weeks. As shown in Tables 3 and 4 and FIGS. 1 and 3, maximum plasma concentrations (C_{maxs}) were also demonstrated in less than about 5 minutes, indicating that C_{maxs} were being approximately obtained by the end of nebulization. The C_{maxs} and AUCs (area under the curve) obtained for the two different dosage strengths were below levels that would induce side effects

due to systemic exposure. Referring to Tables 3 and 4, C_{max} ranged from about 670 pg/ml to about 750 pg/ml, and $AUC_{0\text{-}inf}$ ranged from about 22,000 pg-min/ml to about 33,000 pg-min/ml. These levels are significantly below those found in a clinical study by Murphy et al. (Murphy, K., Noonan, M., Silkoff, P. Uryniak, T., *"A 12 Week Multicenter, Randomized, Partially Blinded, Active Controlled, Parallel-Group Study of Budesonide Inhaltion Suspention in Adolescents and Adults with Moderate to Severe Persistent Asthma Previously Receiving Inhaled Corticosteroids with a Metered- Dose or Dry Powder Inhaler"*, Clinical Therapeutics, Vol. 29, No. 6, pp. 1013-1026, June 2007). Murphy et al.'s dosing regimen of 1.0 mg twice a day (bid) was the same as that for Pulmicort Respules when the pharmacokinetics of Pulmicort Respules was being assessed by Astrazeneca (Pharmacokinetics section of Pulmicort Respules label insert). At the 1.0 mg bid dose, significant safety issues (supression of cortisol) were noted by the FDA. Given that UDB administration resulted in lower C_{max} and AUC values than Murphy et al. (and thus, Pulmicort Respules), while having comparable efficacy, it is believed that side-effects would be reduced due to the lower systemic exposure.

Table 3 Mean pK Parameters For 0.25 mg Dose Budesonide Administered To Asthmatic Children Over Six Weeks

Geometric mean PK parameters (units)	0.25mg	
	First Dose	Day 42
$AUC_{0\text{-}inf}$ (pg-min/mL)	20,849	33,116
T_{max} (min)	3.3	5.0
C_{max} (pg/mL)	320.7	745.9
$T_{1/2}$ (min)	154.6	75.7

Table 4. Mean pK Parameters For 0.135 mg Dose Budesonide Administered To Asthmatic Children Over Six Weeks

Geometric mean PK parameters (units)	0.135mg	
	First Dose	Day 42
$AUC_{0\text{-}inf}$ (pg-min/mL)	10,238	22,071
T_{max} (min)	4.4	4.4
C_{max} (pg/mL)	214.4	672.1
$T_{1/2}$ (min)	42.1	71.3

[0029] Referring to Table 3 and FIG. 2, $AUC_{0\text{-}inf}$ (pg-min/mL) was shown to increase from about 20,849 pg-min/ml at initial dosing to about 33,116 pg-min/ml, about 1.6 times its

value at first dose after repeat dosing of 0.25 mg budesonide for six weeks. C_{max} was shown to at least double after 42 days (six weeks) of dosing.

[0030] Referring to Table 4, the C_{max} for the 0.135 mg dose increased from about 214 pg/ml to about 672 pg/ml from initial dosing to week six of dosing, more than tripling. The corresponding $AUC_{0\text{-}inf}$ more than doubled by week six of dosing. Despite the increase in C_{max} and $AUC_{0\text{-}inf}$, the T_{max} and the ratios of C_{max} to $AUC_{0\text{-}inf}$ remained relatively constant. The T_{max} averaged 4.4 minutes over the 6 weeks for the 0.135mg dose. Within the normal variance between subjects with different ages and weights, the C_{max} to $AUC_{0\text{-}inf}$ ratio remained constant at approximately 0.02 min^{-1} with a standard deviation less than approximately 0.006 min^{-1}. A similar observation may be made for the 0.25 mg dose where the T_{max} averaged 4.1 minutes over 6 weeks, and the C_{max} to $AUC_{0\text{-}inf}$ ratio remained relatively constant at approximately 0.025 min^{-1} with a standard deviation less than approximately 0.007 min^{-1}. Without being bound by theory, it is believed that this indicates that the budesonide is being deposited and absorbed from increasing topical area in the lung over time.

[0031] As a comparative example, Table 5 illustrates the pharmacokinetic response to the administration of budesonide in adults. Here the 0.135 mg dose of budesonide (UDB; provided in the formulation shown in Table 6) corresponded to the 0.25 mg dose for Pulmicort Respules, and the 0.25 mg dose of budesonide (UDB; provided in the formulation shown in Table 6) corresponded to the 0.5 mg dose of Pulmicort Respules in intended therapeutic effect. The $AUC_{0\text{-}inf}$ of the Pulmicort Respules increased about 1.6 times after 7 days (one week) of repeat dosing twice daily, while that of UDB more than tripled. Despite the tripling of the $AUC_{0\text{-}inf}$ for UDB, indicating higher absorption of the budesonide, in no case did the UDB $AUC_{0\text{-}inf}$ s exceed those of corresponding doses of the Pulmicort Respules. This indicates that for comparable lung dosing, there is lower systemic exposure because the UDB doses were at approximately half those of the Pulmicort Respules. Given the large increase of $AUC_{0\text{-}inf}$, it is believed that a similar result would have been obtained in children if measured at one week.

Table 5. Mean pK Parameters For Pulmicort Respules and UDB Administered to Asthmatic Adults Over 1 Week

	Pulmicort Respules			
	Dose 1 (Day 1)		Dose 15 (Day 7)	
	0.25 mg	0.5 mg	0.25 mg	0.5 mg
AUC_{0-inf} (pg-min/ml)	26,900	55,900	45,200	90,100
	UDB			
	Dose 1 (Day 1)		Dose 15 (Day 7)	
	0.135 mg	0.25 mg	0.135 mg	0.25 mg
AUC_{0-inf} (pg-min/ml)	10,300	19,400	35,050	58,700

[0032] An important measure of systemic exposure to corticosteroids is the level of endogenous cortisols in the blood. Excess exogenous corticosteroids will suppress natural production of cortisols due to the suppression of the adrenal cortex. Measurement of adrenocorticotropic hormone (ACTH)-induced plasma cortisol levels in children who were administered budesonide as shown in Tables 3 and 4, showed no evidence of hypothalamus-pituitary-adrenal (HPA) axis suppression by budesonide after six weeks of treatment. Specifically, the data demonstrated a change in median plasma cortisol values over six weeks from 11.0 μg/dl to 11.3 μg/dl for the 0.25 mg budesonide dose, and 10.8 μg/dl to 12.0 μg/dl for the 0.135 mg budesonide dose. Both these changes are statistically insignificant. In sum, these results demonstrated the efficacy and safety (reduced systemic exposure/side-effects) of the budesonide formulations provided in Table 6 when administered twice a day.

[0033] The data from the clinical trial demonstrated that a dose of about 0.30 mg or less of budesonide at least twice a day may result in a pharmacokinetic profile characterized by a T_{max} that is less than about 5 minutes and an AUC_{0-inf} that increases by more than about 1.5 times the AUC_{0-inf} of the initial dose when administered for at least 7 days. Here the pharmacokinetic profile may also be further characterized by a C_{max} to AUC_{0-inf} ratio that remains approximately constant over a predefined time period, a C_{max} of about 850 pg/ml or less, and an AUC_{0-inf} that does not exceed about 75,000 pg-min/ml.

[0034] The data also showed that administering a dose of 0.30 mg or less of budesonide by nebulization twice a day for at least a six week period may result in an AUC_{0-inf} that at least

doubles over the six week period. Such administration may also result in a C_{max} that is less than about 850 pg/ml.

Formulations

[0035] Any corticosteroid formulation suitable for nebulization may be used with the methods described here. Suitable corticosteroids that may be employed include, but are not limited to, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, ciclesonide, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desciclesonide, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino-acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and derivatives, analogues, enantiomer forms, stereoisomers, anhydrides, acid addition salts, base salts, solvates, and combinations thereof. In one variation, the corticosteroid is budesonide.

[0036] The formulations may also include excipients and/or additives. Suitable excipients and/or additives that may be employed include one or more surface active agents, phospholipids, solubility enhancers, surface modifiers, antioxidants, chelating agents, or combinations thereof. Useful surface stabilizers include, but are not limited to, non-ionic surface stabilizers such as polyoxyethylene sorbitan esters and polysorbate 80. Useful phospholipids include without limitation, lecithin NF grades or synthetic phospholipids including lecithin NF, purified lecithin, hydrogenated lecithin, soy or egg lecithin phosphatides containing mixtures of anionic phosphatides such as phosphatidylinositol, phosphatidylserine, phosphatidic acid, phosphatidylglycerol, the corresponding lysophosphatides, synthetic phosphatidic acid, and mixtures thereof. Chelating agents include, but are not limited to, cyclodextrins, cromoglycates, xanthates including caffeine, pegylation agents, crown ethers, ethylenediaminetetraacetic acid

(EDTA) or a salt thereof, such as the disodium salt, citric acid, nitrilotriacetic acid and the salts thereof. Antioxidants include, but are not limited to, vitamins, provitamins, ascorbic acid, vitamin E, or salts or esters thereof.

[0037] Other excipients that may be used, include, but are not limited to, one or more inclusion complexes, pH buffers, tonicity modifiers, binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, wetting agents, disintegrants, and effervescent agents.

[0038] Examples of suitable preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

Exemplary Formulations

[0039] Exemplary formulations that may be used with the methods described here may include budesonide and one or more of a surface active agent, a phospholipid, and EDTA. In some variations, the formulations include micronized budesonide, polysorbate 80, hydrogenated soy lecithin, and EDTA. For example, the formulations may comprise between about 0.0031% to about 0.025% by weight micronized budesonide, between about 0.0001% to about 1.0% by weight polysorbate 80, between about 0.00016% to about 0.00125% hydrogenated soy lecithin, and between about 0.0001% to about 5.0% by weight EDTA. In one variation, the formulation includes about 0.005% by weight EDTA. Exemplary budesonide formulations are shown in Table 6. These formulations may be made by the process described in Example 1.

Table 6. Exemplary Budesonide (UDB) Formulations

Component	**Content Per Unit Dose (0.135 mg budesonide)**	**Content Per Unit Dose (0.25mg budesonide)**
Budesonide, Micronized	0.135 mg	0.250 mg
Polysorbate 80	0.037 mg	0.043 mg
Hydrogenated Soy Lecithin (S75-3)	0.007 mg	0.013 mg
EDTA (Edetate Disodium Dihydrate)	0.075 mg	0.075 mg
Sodium Chloride	12.75 mg	12.75 mg
Sodium Citrate Dihydrate	0.94 mg	0.94 mg
Citric Acid	0.28 mg	0.28 mg
Water for Injection	q.s. to 1.5 ml	q.s. to 1.5 ml

[0040] The invention will be further understood by the following non-limiting examples.

Examples

Example 1: Preparation of Budesonide Formulations

[0041] To form a unit dose budesonide formulation, budesonide particles are initially processed to produce a sterile bulk drug intermediate dispersion, which is further processed into a final aerosol formulation. In the initial processing, the crystalline budesonide starting material is subjected to a milling step to reduce the size of the budesonide particles. The milling step is accomplished by milling crystalline budesonide starting material in a dilute solution of polysorbate 80 (Tween 80) and a milling media to a substantially smaller diameter. The budesonide particles produced are stabilized by the subsequent addition of hydrogenated soy

lecithin and disodium edetate. The resulting concentrated bulk drug intermediate dispersion is then sterilized. The bulk drug intermediate dispersion is further processed into a desired aerosol formulation by diluting it aseptically to the appropriate strength by addition of a sterile citrate-buffered isotonic saline solution. The final pH of the aerosol formulation may be from about pH 4 to about pH 7. It is understood that the amount of sodium citrate or citric acid added for dilution may be modified to produce the desired pH.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method for treating a respiratory condition comprising administering a dose of about 0.30 mg or less of a corticosteroid at least twice a day, wherein administration of the corticosteroid dose results in a pharmacokinetic profile characterised by a T_{max} that is less than about 5 minutes and an $AUC_{0\text{-}inf}$ that does not exceed about 60,000 pg-min/mL when administered for at least 7 days.

2. A method according to claim 1, wherein the pharmacokinetic profile is further characterised by a C_{max} to $AUC_{0\text{-}inf}$ ratio that remains approximately constant over a predefined time period.

3. A method according to claim 1, wherein the pharmacokinetic profile is further characterised by a C_{max} of about 850 pg/mL or less.

4. A method according to claim 1, wherein the corticosteroid is administered for at least 14 days.

5. A method according to claim 1, wherein the corticosteroid is administered for at least 28 days.

6. A method according to claim 1, wherein the corticosteroid is administered for at least 42 days.

7. A method according to claim 1, wherein the corticosteroid is administered for at least three months.

8. A method according to claim 1, wherein the corticosteroid dose is administered by nebulisation.

9. A method according to claim 8, wherein the T_{max} is about the same as the nebulisation time of the corticosteroid.

10. A method according to claim 9, wherein the T_{max} and nebulisation time are each about 5.0 minutes or less.

11. A method according to claim 9, wherein the T_{max} and nebulisation time are each about 4.0 minutes or less.

12. A method according to claim 9, wherein the T_{max} and nebulisation time are each about 3.0 minutes or less.

13. A method according to claim 9, wherein the T_{max} and nebulisation time are each about 2 minutes or less.

14. A method according to claim 1, wherein the corticosteroid is administered in a dose of about 0.22 mg to about 0.27 mg.

15. A method according to claim 1, wherein the corticosteroid is administered in a dose of about 0.10 mg to about 0.15 mg.

16. A method according to claim 1, wherein the corticosteroid is administered in a dose of about 0.25 mg or less.

17. A method according to claim 1, wherein the corticosteroid is administered in a dose of about 0.135 mg or less.

18. A method according to claim 1, wherein the corticosteroid is selected from the group consisting of 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, ciclesonide, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desciclesonide, desonide, desoximetasone,

dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino-acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and derivatives, analogues, salts, and combinations thereof.

19. A method according to claim 18, wherein the corticosteroid is budesonide.

20. A method according to claim 19, wherein the budesonide is administered in a formulation comprising a surface active agent, a phospholipid, EDTA, or a combination thereof.

21. A method according to claim 1, wherein the pulmonary condition is asthma.

22. A method according to claim 1, wherein administration of the dose of the corticosteroid is repeated.

23. A method according to claim 1, wherein the dose of the corticosteroid is administered to a pediatric patient.

24. A method according to claim 1, wherein the dose of the corticosteroid is administered to an adult patient.

25. A method for treating a respiratory condition comprising administering a dose of about 0.30 mg or less of budesonide at least twice a day, wherein

administration of the budesonide dose results in a pharmacokinetic profile characterised by a T_{max} that is less than about 5 minutes, a C_{max} less than about 850 pg/mL, and an $AUC_{0\text{-}inf}$ that does not exceed 60,000 pg-min/mL when administered repeatedly for at least 7 days.

26. A method for treating a respiratory condition comprising administering a dose of 0.30 mg or less of a corticosteroid by nebulisation twice a day for at least a six week period to a patient afflicted with the respiratory condition, wherein the $AUC_{0\text{-}inf}$ of the administered corticosteroid does not exceed about 60,000 pg-min/mL during the six week period, and the T_{max} is less than about 5 minutes.

27. A method according to claim 26, wherein the corticosteroid is selected from the group consisting of 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, ciclesonide, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desciclesonide, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino-acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and derivatives, analogues, salts, and combinations thereof.

28. A method according to claim 27, wherein the corticosteroid is budesonide.

29. A method according to claim 28, wherein the budesonide is administered in a dose of about 0.25 mg.

30. A method according to claim 29, wherein the $AUC_{0\text{-}inf}$ increases from about 21,000 pg-min/mL to about 33,000 pg-min/mL, but does not exceed 60,000 pg-min/mL.

31. A method according to claim 28, wherein the budesonide is administered in a dose of about 0.135 mg.

32. A method according to claim 31, wherein the $AUC_{0\text{-}inf}$ increases from about 10,000 pg-min/mL to about 22,000 pg-min/mL, but does not exceed 40,000 pg-min/mL.

33. A method according to claim 26, wherein the respiratory condition is asthma.

34. A method for reducing one or more systemic side-effects of corticosteroids comprising administering a dose of about 0.30 mg or less of a corticosteroid twice a day for at least six weeks in an aerosol, wherein the $AUC_{0\text{-}inf}$ is less than about 60,000 pg-min/mL, and the T_{max} is less than about 5 minutes.

35. A method according to claim 34, wherein the corticosteroid is budesonide.

36. A method according to claim 34, wherein the systemic side-effect is cortisol suppression.

37. A method according to claim 34, wherein the corticosteroid is administered by nebulisation.

38. A method according to claim 34, wherein the corticosteroid is administered to treat asthma.

5

Dated this 7th day of March 2014

Shelston IP

Attorneys for: MAP Pharmaceuticals, Inc.

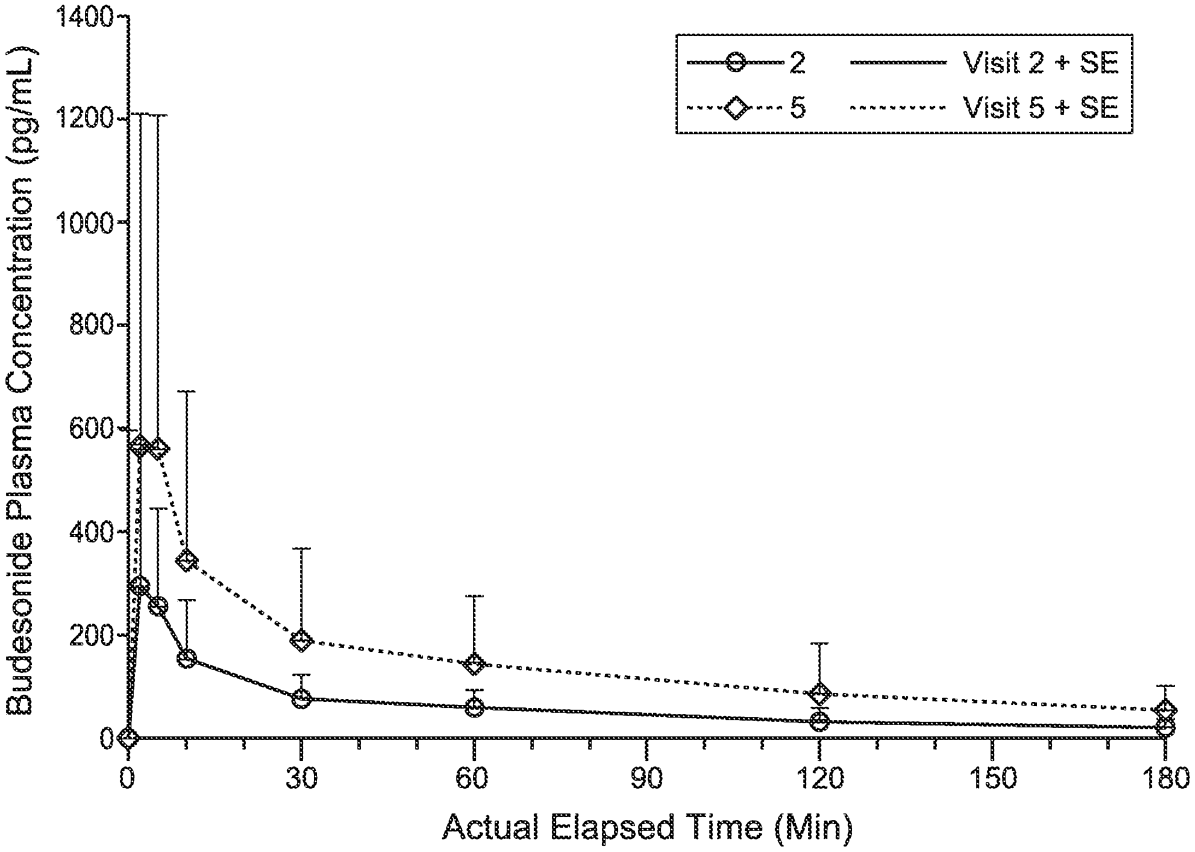
Budesonide Plasma Concentration (pg/mL)
1400
1200
1000
800
600
400
200
0
0
30
60
90
120
150
180
Actual Elapsed Time (Min)
2
Visit 2 + SE
5
Visit 5 + SE

FIG. 1

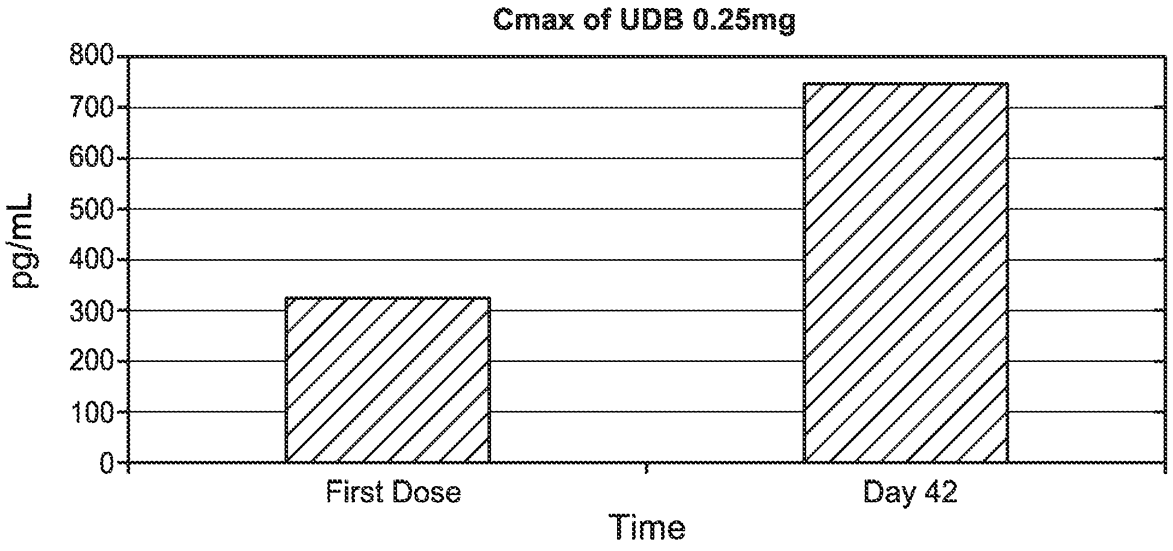
Cmax of UDB 0.25mg
pg/mL
800
700
600
500
400
300
200
100
0
First Dose
Day 42
Time

FIG. 2

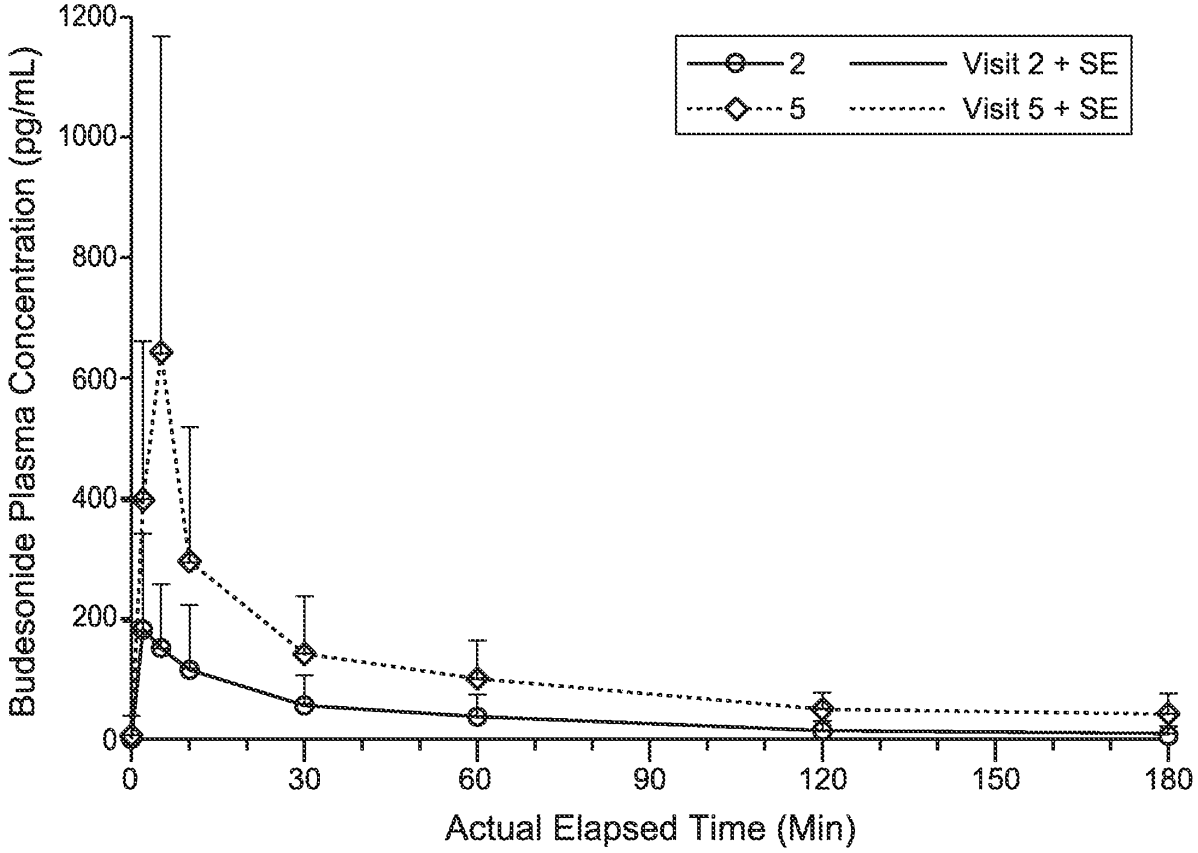
Budesonide Plasma Concentration (pg/mL)
1200
1000
800
600
400
200
0
0
30
60
90
120
150
180
Actual Elapsed Time (Min)
2
Visit 2 + SE
5
Visit 5 + SE

FIG. 3

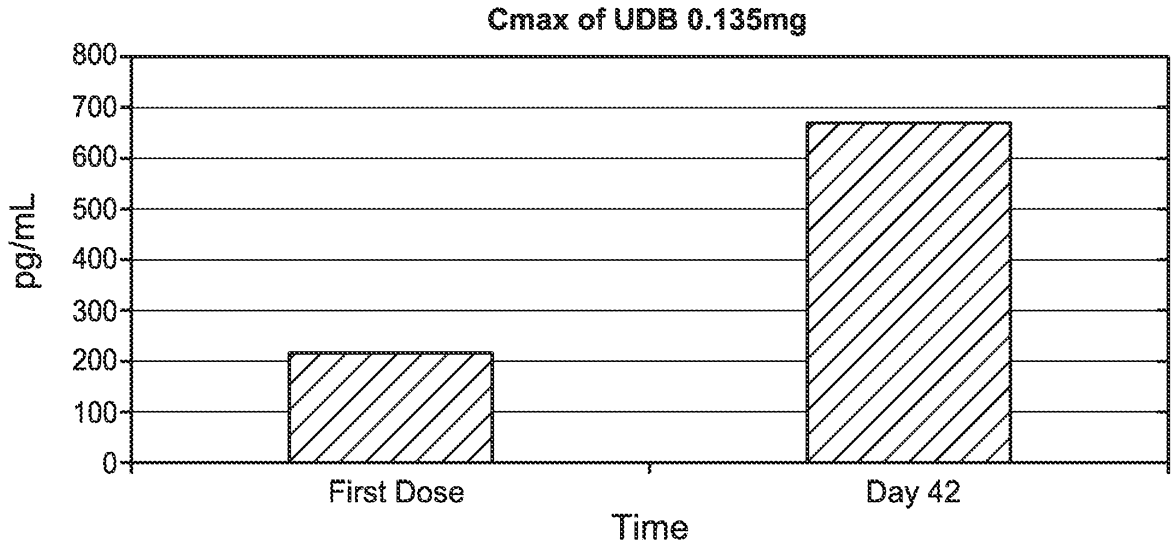
Cmax of UDB 0.135mg
pg/mL
800
700
600
500
400
300
200
100
0
First Dose
Day 42
Time

FIG. 4