Pharmacokinetics and tolerability (Study 1) with particular reference to ocular safety (Study 2) of tiotropium Respimat® Soft Mist™ Inhaler: findings from two dose-ranging studies in healthy men

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Abstract: Data are presented from two randomized, double-blind, placebo-controlled studies in which the tolerability of tiotropium Respimat® Soft Mist™ Inhaler (SMI), a new-generation, propellant-free device for use in COPD, and the ocular safety of tiotropium were examined. In Study 1, 36 healthy males received tiotropium 8, 16, or 32 μg (n = 9/dose) or placebo (n = 3/dose level), administered once daily via Respimat® SMI for 14 days. Safety and pharmacokinetics were evaluated. In Study 2, 48 healthy males received tiotropium 0.02, 0.04, 0.08, 0.16, 0.28, or 0.40 μg (n = 6/dose) or placebo (n = 2/dose level), applied as two drops to one eye (the highest dose was a significant multiple of a percentage of the proposed Respimat® SMI clinical dose that could be inadvertently deposited in the eye). Ocular parameters were measured over 24 hours. Tiotropium Respimat® SMI at doses up to 32 μg was well tolerated in Study 1; typical dose-dependent anticholinergic adverse events of mild-to-moderate intensity were observed. In Study 2, ocular tiotropium administration did not affect pupil diameter, pupillary reflex, intraocular pressure, or accommodation. Tiotropium Respimat® SMI was well tolerated. Inadvertent ocular exposure to tiotropium up to 0.40 μg is unlikely to result in ocular adverse effects.

Keywords: Respimat® Soft Mist™ Inhaler, tiotropium, anticholinergic, chronic obstructive pulmonary disease

Introduction

Inhalation is well established as an effective means of delivering respiratory drugs to the lung. There are currently several inhalation systems available, including pressurized metered-dose inhalers (pMDIs) and dry-powder inhalers (DPIs). However, some propellants and leachables in these inhalers can pose a risk when used in the long term (Markovic 2007). The adverse event profile associated with the inhaled drug should also be taken into consideration when choosing the right inhaler and the correct dose for a patient. For example, inhaled corticosteroids are known to increase oropharyngeal candidiasis and hoarseness (Yang et al 2007), and combined corticosteroid-long-acting β-agonist inhalers can be associated with pneumonia (Nannini et al 2007). For a chronic disease, it is therefore important to find inhaler-drug combinations that are not only effective, but contain safer propellants, and have the potential for minimal drug-related adverse events (ie, dose reduction).

The Respimat® Soft Mist™ Inhaler (SMI) was designed to address many of these issues. The development has been described in detail elsewhere (Zierenberg 1999). In short, it is a propellant-free device that uses a mechanical spring to generate a fine aerosol (the majority of the particle mass is in the region of 1–5 μm), which

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facilitates better deposition of drug in the lung compared with pMDIs and DPIs (Dalby et al 2004; Zierenberg 1999). Primarily, Respimat® SMI has been developed for use with the long-acting anticholinergic tiotropium, which is normally delivered via a DPI (HandiHaler®) (usual dose is 18 μg). The efficacy, safety and pharmacokinetics of tiotropium 18 μg HandiHaler® are well established (Casaburi et al 2002; Brusasco et al 2003; Vincken et al 2002; O'Donnell et al 2004; Niewoehner et al 2005; Kesten et al 2006). Recently published studies with tiotropium Respimat® SMI have shown that lower doses (5 μg and 10 μg) are comparable with tiotropium 18 μg HandiHaler® (Caillaud et al 2007), and superior to ipratropium 36 μg pMDI (Voshaar et al 2008). However, as Respimat® SMI is a novel device with improved lung deposition, it is important to investigate the tolerability of a range of tiotropium doses delivered via this device.

The first aim of this paper was to examine the safety, tolerability and pharmacokinetics of tiotropium (8–32 μg) administered via Respimat® SMI to healthy male subjects (Study 1). The dose-range used was based on findings from an earlier multiple-dose study performed with HandiHaler® (Boehringer Ingelheim data on file), and this range also covers the potential clinical doses to be used with Respimat® SMI (ie, 5–10 μg). A second aim of this paper was to examine the hazards associated with inadvertent ocular exposure to tiotropium. Isolated reports of acute angle-closure glaucoma have been documented for the nebulized short-acting anticholinergic, ipratropium, administered in combination with the β_2-agonist, salbutamol (Shah et al 1992; Hall 1994). To establish the potential for tiotropium to cause inadvertent ocular side effects, an ocular safety study (Study 2) was initiated in which tiotropium drops (up to 0.4 μg) were administered directly to one eye of healthy male volunteers. The highest dose was a significant multiple of a percentage of the proposed Respimat® SMI clinical dose (ie, 5–10 μg) that could be inadvertently deposited in the eye.

Materials and Methods

Study design

The first single-center study (Study 1; 205.112) examined the safety, tolerability, and pharmacokinetics of three increasing doses (8, 16, and 32 μg) of tiotropium administered via Respimat® SMI (Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany). This was a randomized, double-blind (within-dose-groups), placebo-controlled design. The planned sample size was 36 volunteers, based on 3 sequential groups of 12 subjects each (n = 9/dose, n = 3/placebo). The second single-center study (Study 2; 205.138), which investigated the effects of inadvertent ocular exposure to tiotropium, also followed a randomized, double-blind (within-dose-groups), placebo-controlled design. The planned sample size was 48 volunteers, based on 6 sequential groups of eight subjects each (n = 6/dose, n = 2/placebo). The studies were performed according to the Declaration of Helsinki and both protocols were approved by the Ethics Committee of the local Medical Council, Mainz, Germany. All participants provided written informed consent prior to participation.

Inclusion and exclusion criteria

Participants in both studies were healthy males aged between 21 and 43 years. Subjects were excluded if the results of a medical examination or laboratory tests were judged by the clinical investigator to differ significantly from normal clinical values. Subjects were excluded if they had gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, hormonal, psychiatric, or neurological disorders, or any other condition deemed relevant to the study by the trial investigator. Other exclusion criteria included: concomitant use of any drug that might influence results of the trial; significant alcohol or drug abuse; and heavy smoking or the inability to refrain from smoking during the study. For the ocular safety study, additional exclusion criteria included: known eye diseases, such as glaucoma; hyperopia (>3 dioptries); contact lens use; intraocular pressure >22 mm Hg; predisposition to narrow-angle glaucoma; and disturbed micturition.

Interventions

Following screening, subjects in Study 1 were randomized to receive placebo or tiotropium delivered via Respimat® SMI once daily for 14 days. Treatment (one inhalation) was given 1 hour after a light breakfast by the investigating physician, and subjects inhaled the mist through the mouth while their nostrils were clamped. The inhalation doses initially planned (8–64 μg) were based on dose levels used in an earlier multiple-dose study performed with HandiHaler® (Boehringer Ingelheim data on file), and they also reflect the potential clinical dose ranges to be used with Respimat® SMI (ie, 5–10 μg). If there were no side effects with one dose tested, then a new group of subjects received the next higher dose after an interval of at least 1 week. Blinding was maintained at each stage. However, after completion of the tiotropium 32 μg 14-day intervention, the incidence of anticholinergic adverse effects led to the replacement of the planned 64 μg dose level by a 16 μg dose. Hence, the different doses were tested consecutively in the order 8, 32, and 16 μg.

Subjects in Study 2 were randomized to receive either placebo or a single dose of tiotropium 0.02, 0.04, 0.08, 0.16, 0.28, or 0.40 μg applied as 2 drops (total volume 50 μl) to 1 eye by the investigating physician. Blinding was maintained in each dose group. The dose range selected took into account (i) the dose range for inhalation that is planned for clinical studies (ie, 5–10 μg), (ii) that approximately 1% (worst case) of a dose fired from the Respimat® SMI device directly into the eyes could be deposited in the area of both eyes during misuse of the inhaler, and (iii) was also based on animal models, which showed that administration of doses up to 0.40 μg did not result in mydriasis.

Assessments

In Study 1, a general medical examination, which included physical and laboratory tests and an electrocardiogram (ECG), was carried out at screening (a maximum of 14 days before the first inhalation [study day 1]) and within 8 days after the last study day. Standard laboratory tests (including hematological analysis, urinalysis, and serum chemistry), blood pressure, pulse, respiratory rate, and 12-lead ECG were recorded during screening, before dosing, and 25 minutes after medication on days 1, 7, and 14, as well as on the morning of day 15 and within 8 days of the final inhalation. Salivary secretion was measured before and 35 minutes after drug administration on days 1, 7, and 14 using the difference in weight of 4 cotton rolls placed in the oral cavity before and after drug administration. Adverse events were monitored throughout the study.

Blood for determination of plasma tiotropium concentration was taken before each daily inhalation, and 5 and 20 minutes after inhalation on days 1, 7, and 14. Urine was collected during the intervals 0–4 hours, 4–8 hours, and 8–24 hours after inhalation on days 1, 7, and 14. Quantitative determination of tiotropium in plasma and urine was achieved using a reverse high-pressure liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) assay using electrospray ionization and multiple reaction monitoring. Airway resistance was evaluated before daily inhalation and 1 hour after inhalation on days 1, 7, and 14 using whole body plethysmography.

In Study 2, primary endpoints were pupillary diameter and pupillary reflex, intraocular pressure, and accommodation. Secondary endpoints included vital signs, 12-lead ECG, adverse events, and standard laboratory evaluations. All ocular measurements were taken at screening and on the treatment day (before and 1, 4, 8, and 24 hours after dosing). Pupillary reflex of the treated eye was also measured 15, 30, and 45 minutes after dosing. Vital signs and 12-lead ECG measurements were taken at screening and on the treatment day (before treatment and after 24 hours). Adverse events were monitored throughout the study. Local tolerability of the eye – examined by assessing the presence of swelling, induration, calor, rubor, and pain caused by pressure – was included as part of the adverse-event monitoring. In addition, subjects were asked to report any feelings of warmth, itching, or spontaneous pain. The intensity of any subject-reported symptom was scored as being mild, moderate, or severe. All adverse events were monitored until they had normalized or had been sufficiently characterized. A follow-up visit, which included medical examination, laboratory examination, 12-lead ECG, blood pressure, and pulse rate took place within 8 days of treatment.

Pharmacokinetics

For quantitative analysis of tiotropium in Study 1 analytes were extracted from plasma and urine using solid-phase and liquid/liquid extraction. Tiotropium was finally analyzed using HPLC-MS/MS (PE Sciex API III HPLC MS/MS system). The chromatographic separation of the analytes was achieved by reverse phase liquid chromatography using a C_{18} stationary phase (Kromasil 100 C_{18}, 125 × 1.6 mm, 5 μm). An electrospray ion source (atmospheric pressure ionization) was used for ionization. The HPLC assays for plasma and urine samples were revalidated prior to sample analysis in the range 3.24–108 pg/mL and 58.5–1288 pg/mL tiotropium bromide monohydrate, respectively. The lower limits of quantification for the active drug (tiotropium cation) were 2.59 pg/mL in plasma and 11.0 pg/mL in urine. The coefficient of variation was between 6.2% and 8.8% for plasma samples, and between 4.5% and 6.4% for urine samples.

Plasma concentrations were used to derive the maximum and predose drug plasma concentrations (C_{max} and C_{pre}), the area under the tiotropium plasma concentration–time curve from the time of inhalation to 20 minutes postdose ($AUC_{0–20min}$); this timeframe was identical to an earlier study performed with a different inhalation device (Boehringer Ingelheim data on file). Tiotropium concentrations in urine were used to calculate the amounts excreted unchanged in the urine over a defined time period ($Ae_{t1–t2}$; t1 = start of sampling interval, t2 = end of sampling interval).

Statistical analysis

For the safety variables, standard statistical parameters or frequency tables were calculated. All adverse events were listed and summarized in tables using the World Health

Organization Adverse Reaction Terminology List (WHO-ARTL)-preferred terms and compared between treatments.

Results

Study 1

Safety and tolerability of tiotropium administered via Respimat® SMI

A total of 36 healthy male subjects received treatment in Study 1; of these, 27 subjects received tiotropium (9 per dose group) and 9 subjects received placebo (3 per dose group). Baseline characteristics were comparable across all groups; the mean age of participants treated with tiotropium was 30.5 years (range: 21–43 years), the mean height was 180 cm (range: 169–199 cm), and the mean body weight was 78.7 kg (62–102 kg). All participants were Caucasian.

No clinically relevant effects on respiratory rate and pulse rates, blood pressure, or ECG were observed during the 14 days of tiotropium treatment. No drug-related changes were recorded for any of the laboratory parameters measured (hematology, clinical chemistry, and urinalysis). One subject (treated with tiotropium 32 μg) discontinued the study on day 9 for reasons unrelated to treatment. Transient dose-related anticholinergic adverse events were observed approximately 1 week after treatment was initiated: 2, 5, and 14 events of mild-to-moderate dry mouth/throat and dry nasal mucosa were reported in subjects who received tiotropium 8, 16, and 32 μg, respectively (Table 1). No subjects who received placebo reported anticholinergic side effects. A marked reduction in unadjusted salivary flow was observed from day 1 (baseline) to day 7 in the group of subjects receiving tiotropium 32 μg (Figure 1); however, there was such a variation of mean data points on day 1 that it was difficult to interpret these results. No serious adverse events were reported throughout the study.

Table 1 Most commonly reported adverse events following inhalation of tiotropium (Study 1)

	Tiotropium 8 μg	Tiotropium 16 μg	Tiotropium 32 μg
Headache	2	1	2
Dryness of nasal mucosa	1	3	5
Dryness of mouth/palate	1	2	6
Dryness of throat			3
Common cold	1	2	1
Difficulty in swallowing			3
Bitter taste			2
Herpes labialis	2		
Irritation of throat			1
Irritation of conjunctiva	1		1
Tiredness	1		

Airway resistance after administration of tiotropium via Respimat® SMI

Airway resistance showed a slight decrease during the study, which was not dose-dependent and not statistically significant. None of the healthy volunteers reported any respiratory symptoms.

Pharmacokinetics of tiotropium administered via Respimat® SMI

Tiotropium plasma concentrations increased rapidly after inhalation, with the highest tiotropium concentration (C_{max}) generally observed in the blood sample collected 5 minutes after inhalation ($C_{max} = C_{5min}$) (Figure 2). The tiotropium plasma concentration decreased within 20 minutes afterwards to about 60%–70% of the maximum value. The systemic exposure to tiotropium was proportional to the dose inhaled; for example, the C_{5min} for tiotropium 8 μg and 32 μg was 4.23 and 22.1 pg/mL on day 1, respectively. The C_{5min} increased between day 1 and day 7 by a factor of approximately 2 for all tiotropium doses, and between day 1 and day 14 by approximately 2- to 3-fold (Table 2). Thus, the increase in C_{5min} from day 7 to day 14 was about 1- to 1.5-fold.

Geometric mean tiotropium plasma concentrations measured before inhalation showed a dose-related increase on all study days, similar to that observed for C_{5min} (Table 2). In contrast to the C_{5min} values; however, the plasma concentrations before inhalation on day 14 compared with day 7 for the 16 and 32 μg doses were still approximately 2-fold higher, suggesting that steady state had not been fully achieved within 7 days (Table 2).

$AUC_{0–20min}$ values showed a similar trend to that observed for C_{5min} (Table 2); however, a high number of unquantifiable plasma concentrations for the lower doses (8 and 16 μg) resulted in no $AUC_{0–20min}$ calculations on day 1. The geometric mean $AUC_{0–20min}$ values for tiotropium 32 μg increased 3-fold from 4.78 pg•h/mL^{-1} (day 1) to 14.4 pg•h/mL^{-1} (day 14).

Urinary excretion of tiotropium administered via Respimat® SMI

The cumulative amount of urinary tiotropium excreted (in percent of dose) remained similar between doses on each day; approximately 25% of the dose was excreted at steady state (Figure 3). The fraction excreted in urine within 24 hours ($Ae_{0–24h}$) increased between day 1 and day 7 by a factor of about 2–3, but remained similar on day 14 compared with

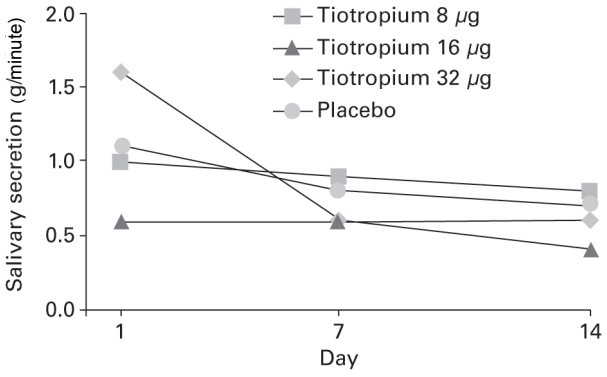

Figure 1 Mean salivary secretion (g/minute) 35 minutes after dosing on days 1, 7, and 14 (Study 1).

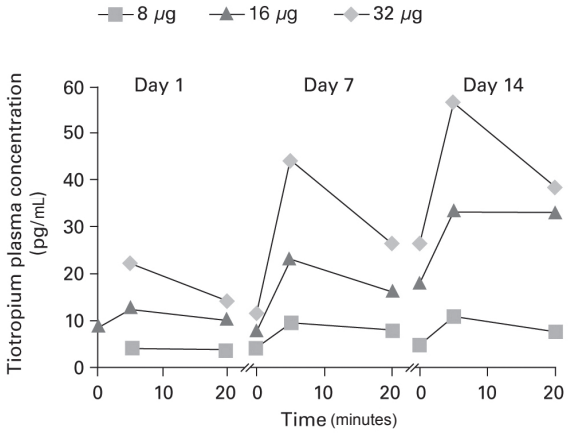

Figure 2 Geometric mean tiotropium plasma concentrations on days 1, 7, and 14 (Study 1).

day 7. The majority of the urine excretion occurred within the first sampling interval (0–4 hours).

Study 2

Safety after tiotropium administration to the eye

A total of 48 healthy male subjects received treatment. The baseline characteristics were comparable across the six treatment groups. Overall, the mean age was 32 years (range: 24–44 years), the mean height was 179 cm (range: 164–194 cm), and the mean weight was 80 kg (range: 58–95 kg). All participants were Caucasian.

Neither the pupil diameter nor the pupillary reflex was influenced by single doses of tiotropium up to 0.40 μg administered as eye drops into the eye. No clinically relevant findings or changes in intraocular pressure were observed, and there was no change in accommodation in any subject. Swelling, induration, and erythema were not observed in any subject. Twenty-five percent of subjects treated with tiotropium (9/36) and of those treated with placebo (3/12) reported a mild burning sensation in the treated eye. This sensation was transient (lasting less than 5 minutes) in all subjects. No subjects required any form of treatment or follow-up. Additionally, 2 subjects, 1 receiving tiotropium and 1 receiving placebo, reported a mild sensation of dryness in the eye. One subject receiving tiotropium 0.40 μg reported a mild subjective sensation of increased intraocular pressure in the treated eye, although objective measurements of intraocular pressure in this subject showed no increase. The incidence of adverse effects was not dose-related. No clinically relevant changes in vital functions, 12-lead ECG, or standard laboratory parameters were observed.

Discussion

The aim of this early phase, placebo-controlled inhalation study was to determine the safety, tolerability, and pharmacokinetics of increasing doses of tiotropium administered via the Respimat® SMI in healthy male volunteers. In addition, data are presented from a separate ocular study investigating the safety of tiotropium when administered to the eye.

The results show that tiotropium administered via Respimat® SMI at increasing doses up to 32 μg was well tolerated. The only clinically meaningful adverse events were dryness of the mouth/throat and nasal mucosa. These typical anticholinergic adverse events were dose-dependent and led to a reduction in the final dose that was evaluated, from the originally planned 64 μg dose to 16 μg. Anticholinergic events, such as those observed in this study, arise through the blockade of muscarinic receptors located on tissues in addition to the airway smooth muscle, and are a common occurrence with inhaled antimuscarinic therapies. Long-term studies with tiotropium indicate that the incidence of these mild anticholinergic side effects does not result in discontinuation of medication in COPD patients (Casaburi et al 2002). Although there was no positive control in this safety study, a subsequent crossover study, in which tiotropium 5–10 μg Respimat® SMI was compared with tiotropium18 μg HandiHaler®, has shown that systemic exposure was comparable for tiotropium 5 μg Respimat® SMI and tiotropium18 μg HandiHaler® in COPD patients (Van Noord et al 2006).

A previous study has shown that peak plasma concentrations of tiotropium are measured 5 minutes after the drug has been inhaled via HandiHaler® (Barnes 2004; Disse et al 1999). Furthermore, tiotropium 18 μg inhaled via HandiHaler® resulted in a C_{5min} of 14 pg/mL (approximately 30 pM). In the current study, peak plasma concentrations were also achieved 5 minutes after tiotropium inhalation

Table 2 Pharmacokinetic parameters of tiotropium determined from plasma concentrations on days 1, 7, and 14 after once-daily inhalation of tiotropium 8, 16, and 32 μg Respimat® (Study 1)

	Tiotropium 8 μg (n = 9)		Tiotropium 16 μg (n = 9)		Tiotropium 32 μg (n = 9)	
	gMean	% gCV	gMean	% gCV	gMean	% gCV
Day 1						
C_{5min} (pg/mL)	4.23	37.8	12.5	28.9	22.1	60.2
$AUC_{0–20min}$ (pg•h/mL^{-1})	NC		NC		4.78	51.4
Day 7						
C_{pre} (pg/mL)	4.05	77.7	7.81	27.5	11.7	50.6
C_{5min} (pg/mL)	9.51	46.8	23.2	23.7	44.2	63.1
$AUC_{0–20min}$ (pg•h/mL^{-1})	3.74	62.3	6.10	22.0	10.4	59.4
Day 14						
C_{pre} (pg/mL)	4.75	69.0	17.9	34.5	26.7	56.4
C_{5min} (pg/mL)	11.0	68.0	33.3	33.1	56.5	50.3
$AUC_{0–20min}$ (pg•h/mL^{-1})	3.64	63.3	10.6	17.8	14.4	53.5

Notes: NC, not calculated; n = 9 unless otherwise indicated; gMean, geometric mean; % gCV, % geometric coefficient of variation; $AUC_{0–20min}$, area under the curve from 0 to 20 minutes; C_{pre}, plasma concentration before inhalation; C_{5min}, plasma concentration 5 minutes after inhalation.

across all dose ranges. For the tiotropium 16 μg dose, a C_{5min} of 12.5 pg/mL was measured on Day 1, which suggests comparability with the earlier study. In this previous paper, the authors also suggested that tiotropium 30 pM is likely to correspond to a receptor occupancy of about 6%; peak concentrations of 9 nM (which are not achievable with inhaled doses) would be needed to achieve 95% receptor occupancy (Disse et al 1999). Such low receptor occupancy may, in part, explain why tiotropium is associated with a rising baseline, with pharmacodynamic steady state (trough FEV_1 and trough FVC) usually being reached within two weeks. Regarding the achievement of pharmacokinetic steady state, trough plasma concentrations in the current study suggest that steady state had not been achieved before Day 14 for all doses tested despite urinary excretion remaining stable after Day 7.

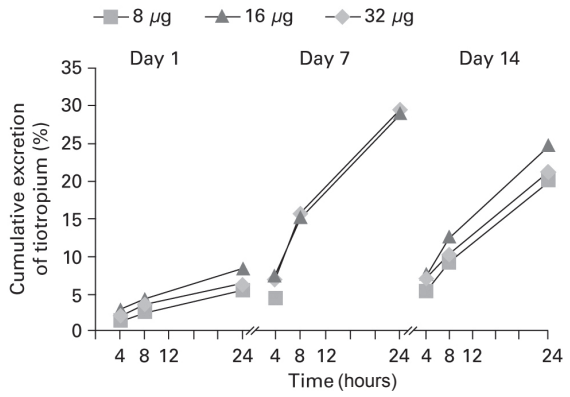

Figure 3 Geometric mean cumulative tiotropium urinary excretion fraction on days 1, 7, and 14 after once-daily inhalation of tiotropium 8, 16, or 32 μg via Respimat® (n = 9/dose) (Study 1).

In the current study, excretion of tiotropium via the urine was slower than has been observed in studies involving intravenous administration (Türck et al 2004), indicating a slower disposition of drug after inhalation compared with infusion. This was also expected, given that elimination via the kidney is very rapid after an initial high load by intravenous infusion, whereas there might be a delay before tiotropium administered via inhalation is released into systemic circulation. Despite a slower excretion when tiotropium is inhaled, previous pharmacokinetic studies show that little of the drug is absorbed (Barnes 2004).

The plasma concentrations of tiotropium and amount excreted in the urine in this study were higher than those observed in previous studies where similar doses of tiotropium were administered via a DPI (Boehringer Ingelheim data on file). Taken together, these results indicate that tiotropium administered via the Respimat® SMI has approximately a 1.5- to 2.5-fold higher bioavailability than similar doses administered using a dry-powder device. This highlights the efficiency of Respimat® SMI in scintigraphy studies (Pitcairn et al 2005, Newman et al 1996); however, the clinical implications of this need further evaluations in studies involving COPD patients.

With respect to the ocular safety findings, case reports of inadvertent administration of active compounds to the eye after use of inhaled anticholinergics have raised concerns about possible deleterious effects (Shah et al 1992; Hall

1994). There is one case report of acute angle-closure glaucoma that may have been precipitated by the patient touching a predisposed eye with papillary dilation after inhalation of tiotropium (Oksuz et al 2007). In the current ocular safety study, no anticholinergic ocular side effects were observed when tiotropium was instilled into the eye at doses many times higher than would realistically enter the eye, even with inhaler misuse. This indicates that there are no obvious risks of anticholinergic side effects associated with inadvertent exposure of the eye to tiotropium at doses up to 0.40 μg. A previous in vitro scintigraphy study also showed that the potential for ocular side effects from tiotropium Respimat® was low; when the Respimat® soft mist was released near the upper face, the eye deposition was low (approximately 0.6% of ex-valve dose, the worst-case deposition was 1%) (Newman et al 2007). However, physicians would be best advised to instruct their patients to wash their hands and avoid touching their eyes after use of any inhaler containing anticholinergics, including tiotropium.

Another important ocular safety concern relates to the elderly; older patients (ie, those more likely to have COPD) may exhibit age-related altered sensitivity to anticholinergics. This could have consequences for visual acuity, which may impact on everyday functions such as driving. The Department for Transport highlights the lack of data in this area as a potential concern relating to older drivers (Holland et al 2003). Although older patients may be more sensitive to the effects of anticholinergics, there was no evidence of ocular problems in this study of healthy volunteers aged up to 44 years.

Conclusions

In conclusion, tiotropium delivered via the Respimat® SMI within a dose range of 8–32 μg once daily for 14 days was well tolerated in healthy volunteers. Ocular administration of tiotropium 0.40 μg is unlikely to result in ocular adverse effects such as changes in pupil diameter, pupillary reflex, intraocular pressure, or accommodation. This low dose is equivalent to a significant multiple of a percentage of the proposed Respimat® SMI clinical dose (ie, 5–10 μg) that could be inadvertently deposited in the eye.

Disclosures

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