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A comprehensive non-clinical evaluation of the CNS penetration potential of antimuscarinic agents for the treatment of overactive bladder

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- This study provides antimuscarinic agents for overactive bladder (OAB) display variable association with side effects mediated by the central nervous system (CNS), which may be of particular concern in the elderly.
- Adverse effects on CNS functioning are related to muscarinic receptor subtype selectivity and the ability of the agent to cross the blood–brain barrier, where P-gp plays a role in limiting permeability.

WHAT THIS STUDY ADDS

- This study provides a parallel investigation of CNS penetration of antimuscarinic OAB agents *in vivo* and assessment of physical properties and permeability in cell monolayers *in vitro*.
- It adds further understanding of the roles of passive transcellular permeability and P-gp in determining CNS penetration of antimuscarinic OAB agents.
- It also enables a comparison of CNS side-effect profiles of OAB agents with preclinical CNS penetration data.

AIMS

To assess and compare the mechanisms of central nervous system (CNS) penetration of antimuscarinic overactive bladder (OAB) agents.

METHODS

Physical properties were computed or compiled from the literature. Rats were administered 5-hydroxymethyl tolterodine (HMT), darifenacin, oxybutynin, solifenacin, tolterodine or trospium subcutaneously. At 1 h postdose, plasma, brain and cerebrospinal fluid (CSF) concentrations were determined using LC-MS/MS assays. Brain and plasma protein binding were determined *in vitro*. Permeability in the presence and absence of the efflux transporter P-glycoprotein (P-gp) was assessed in RRCK and MDCK-MDR1 transwell assays.

RESULTS

Oxybutynin displayed extensive CNS penetration, with brain : plasma ratios (B : P), unbound brain : unbound plasma ratios (Kp,free) and CSF : free plasma ratios each >1. Tolterodine (B : P = 2.95, Kp,free = 0.23 and CSF : free plasma = 0.16) and solifenacin (B : P = 3.04, Kp,free = 0.28 and CSF : free plasma = 1.41) showed significant CNS penetration but with some restriction from CNS as indicated by Kp,free values significantly <1. 5-HMT, darifenacin and trospium displayed much lower B : P (0.03–0.16), Kp,free (0.01–0.04) and CSF : free plasma (0.004–0.06), consistent with poor CNS penetration. Permeability in RRCK cells was low for trospium (0.63×10^{-6} cm s^{-1}), moderate for 5-HMT (11.7×10^{-6} cm s^{-1}) and high for darifenacin, solifenacin, tolterodine and oxybutynin ($21.5–38.2 \times 10^{-6}$ cm s^{-1}). In MDCK-MDR1 cells 5-HMT, darifenacin and trospium, were P-gp substrates, whereas oxybutynin, solifenacin and tolterodine were not P-gp substrates.

CONCLUSIONS

Brain penetration was low for antimuscarinics that are P-gp substrates (5-HMT, darifenacin and trospium), and significant for those that are not P-gp substrates (oxybutynin, solifenacin and tolterodine). CNS adverse events reported in randomized controlled clinical trials show general alignment with the preclinical data described in this study.

Introduction

Overactive bladder (OAB) is a syndrome defined by the International Continence Society as urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia [1]. OAB affects at least 10% of the adult population [2] and the prevalence increases with age [3]. Postulated aetiologies for this condition include increased afferent activity, decreased inhibitory control and increased sensitivity of the detrusor muscle to efferent stimulations [4, 5]. Muscarinic receptors are thought to mediate the detrusor contractions of normal voiding, but in OAB the muscarinic receptors are associated with bladder contraction leading to urinary frequency, urgency and urgency incontinence. Antimuscarinic agents, such as darifenacin, oxybutynin, solifenacin, trospium, tolterodine and fesoterodine have consistently demonstrated significant efficacy for the treatment of OAB symptoms [6, 7]. However, treatment is associated with typical anticholinergic side effects such as dry mouth, constipation, somnolence and blurred vision. The adverse effects (AEs) of antimuscarinic drugs may occur because muscarinic receptors are located throughout the body [8] where inhibition of specific receptor subtypes is associated with side effects. For example, in the central nervous system (CNS), muscarinic receptors, particularly the M_1 subtype, are thought to play an important role in the consolidation of long-term memory. Cognitive impairment is associated with anticholinergic therapy in the elderly [9] and the side-effect profiles seen with some antimuscarinic OAB drugs are consistent with inhibition of muscarinic receptors in the CNS [10]. Although the incidence of CNS AEs of antimuscarinic agents is generally much lower than that of dry mouth [6, 7], CNS AEs can be of great concern, particularly in the elderly [11]. The incidence of CNS AEs among the available antimuscarinic agents for OAB seems to differ. For instance, while darifenacin has been shown to have no significant effects on memory *vs.* placebo, oxybutynin ER caused significant memory deterioration which was deemed comparable with brain ageing of 10 years [12]. The ability of certain antimuscarinic OAB drugs to exert CNS-related pharmacological effects at therapeutic doses for OAB treatment depends on their ability to penetrate the CNS as well as relative affinity for relevant muscarinic receptor subtypes in the CNS, particularly M_1 [13–15]. CNS penetration of drugs depends on the permeability properties of the blood–brain barrier (BBB) [16, 17] and the influence of active efflux transporters present in brain tissue, such as P-glycoprotein (P-gp) [18, 19]. Therefore, the relative permeability and affinity of OAB agents for P-gp is an important consideration in understanding their potential to exert AEs manifested in the CNS.

The purpose of the present paper was to present a comprehensive set of non-clinical *in vitro* and animal studies that investigated in parallel the CNS penetration potential of antimuscarinic OAB drugs. The following studies were conducted: (i) physicochemical characterization, including lipophilicity; (ii) *in vitro* RRCK cell passive permeability assessment; (iii) *in vitro* P-gp mediated efflux in MDCK-MDR1 transcellular flux assay; and (iv) *in vivo* brain, plasma and CSF concentrations following a single subcutaneous dose in rats. Strategies for assessment of brain penetration of compounds have focused on determination of unbound brain : unbound plasma concentration ratios (Kp,free), and consideration of the involvement of transporter proteins at the BBB, in particular P-gp [19]. Therefore, to understand further CNS disposition, the unbound brain : unbound plasma concentration ratios were estimated using brain and plasma binding experiments *in vitro* [19, 20]. The overall aim of this package of data was to enable an understanding of the brain penetration potential of antimuscarinic OAB drugs in relation to their physicochemical and permeability properties. The antimuscarinic agents included in these studies were 5-hydroxymethyl tolterodine (5-HMT, the active metabolite of tolterodine as well as fesoterodine), darifenacin, oxybutynin, solifenacin, tolterodine and trospium. Fesoterodine is a pro-drug that is rapidly and extensively converted to 5-HMT by esterases *in vivo*, and is not detectable after oral administration [21, 22]. Therefore, 5-HMT was evaluated as the relevant active moiety of fesoterodine in this study.

Methods

Materials

Oxybutynin, N-methylscopolamine HBr and atropine (internal standard) were purchased from Sigma-Aldrich. 5-hydroxymethyl tolterodine (5-HMT), solifenacin and trospium chloride were purchased from Toronto Research Chemicals Inc. (Ontario, Canada).

Fesoterodine and scopolamine were obtained from Pfizer Global Research and Development central compound stores (Milwaukee, WI, USA). Tolterodine was purchased from Sequoia Research Products (Pangbourne, UK). Darifenacin was purchased from Toronto Research Chemicals Inc. (Ontario, Canada) and Sequoia Research Products (Pangbourne, UK). Hanks's balanced salt solution (HBSS), cell culture media and supplements were purchased from Invitrogen (Paisley, UK). All other reagents were obtained from Sigma-Aldrich (Poole, UK) or J.T. Baker (Phillipsburg, NJ, USA).

Assessment of physical properties of compounds

The definitions of physical properties of compounds were: log D, logarithm of the distribution coefficient between octanol and buffer at pH 7.4; clog P, logarithm of the calculated partition coefficient between octanol and water, polar surface area (PSA), the area of molecular surface belonging to polar atoms (units: $Å^2$) [17], rotatable bond

count, count of all non-terminal single bonds and hydrogen bond acceptor and donor counts, counts of all atoms in a molecule that are potentially involved in a hydrogen bond as acceptor or donor atoms, respectively. All calculated parameters were determined within the proprietary Pfizer database (RGate), where clog P was determined using the BioByte program clog P, version 4.3 and PSA using a published method [17]. Log D values were taken from published sources [23].

Monolayer efflux studies in MDCK (Madin-Darby canine kidney) and RRCK cell lines

MDCK-MDR1 expressing P-gp were originally obtained from Netherlands Cancer Institute (Amsterdam, the Netherlands). RRCK cells were generated in house (Pfizer Inc., Groton, MA, USA) as a subclone of MDCK wild-type (MDCK-WT) cells that displayed low expression of endogenous P-gp (approximately 1–2% of MDCK-WT cells, based on mRNA level). The rank order of permeability values for compounds whose transcellular flux was predominantly by passive diffusion were similar for RRCK and MDCK-WT (data not shown). Monolayer efflux studies were conducted as previously described in the literature for MDCK-MDR1 cells [24]. Cells were cultured in minimal essential medium α with supplements and passaged when 70–80% confluent. Cell monolayer flux studies were conducted 5 days after seeding in 24-well transwell inserts [MDCK-MDR1 in 0.4-μm pore size (Corning Costar) at 1.8×10^5 cells cm^{-2}; RRCK in 1-μm pore size (Becton Dickinson, Cowley, UK) at 4.2×10^4 cells cm^{-2}]. Donor and acceptor solutions were prepared from HBSS, containing HEPES at 20 mM, pH 7.4. Stock solutions of test compounds were prepared at 10 mM in dimethyl sulphoxide (DMSO) and used to prepare donor solutions of 2 μM compound in 0.05% (v/v) DMSO and also containing 2 μM nadolol used as monolayer integrity marker. Apparent permeability (P_{app}) of compounds was determined in apical to basolateral (A→B) and basolateral to apical (B→A) directions in triplicate by incubation with compound for 2 h at 37°C. Samples of medium (20 μl) from both donor and acceptor chambers were analysed by tandem liquid chromatography and mass spectrometry (LC/MS-MS). The LC/MS-MS system consisted of a 2.1 × 15 mm C18 optilynx column (Optimize Technologies Inc., Oregon city, OR, USA) in line with Onyx monolithic C18 column 50 × 4.6 mm (Phenomenex, Torrance, CA, USA) operating at a flow rate of 3 ml min^{-1}. The aqueous mobile phase consisted of 90% 2 mM ammonium acetate, 10% methanol, 0.1% formic acid. The organic mobile phase was 10% 2 mM ammonium acetate, 90% methanol, 0.1% formic acid. Mass spectrometry was performed on a SCIEX API 4000 triple quadrupole mass spectrometer (Applied Biosystems, Ontario, Canada), with turbo ion spray source. Data were acquired in positive ion mode with an ion spray probe voltage of 5.5 kV. The following selected reaction monitoring transitions, given as mass : charge ratio (m/z) were used to measure the compounds: tolterodine m/z 310→201 and nadolol m/z 310→254 at collision energy of 25 eV; darifenacin m/z 427→147, oxybutynin m/z 358→124, 5-HMT m/z 342→223, fesoterodine m/z 412→223 and nadolol m/z 310→201 at a collision energy of 40 eV; solifenacin m/z 364→110, trospium m/z 392→182 and nadolol m/z 310→56 at a collision energy of 55 eV.

P_{app} values were calculated according to the equation $P_{app} = (Q/t) \times 1/C_0 \times 1/A$, where Q is the sampled concentration in the acceptor compartment, t incubation time; C_0 is the initial concentration in the donor compartment and A is the area of the filter of the transwell plate. Monolayers with nadolol P_{app} values of less than 1×10^6 cm s^{-1} were deemed intact.

In vivo *brain penetration study*

All procedures performed on animals were in accordance with US federal regulations and established NIH guidelines and were reviewed and approved by the Institutional Animal Care and Use Committee. Male Sprague-Dawley rats weighing approximately 250 g ($n = 3$) received a single dose of compound subcutaneously (0.3 or 1 mg kg^{-1}). Dosing solutions were prepared fresh in saline on the day of the study and were administered at 1 ml kg^{-1}. At 1 h postdose, animals were euthanized using CO_2 and approximately 3 ml of blood removed by cardiac puncture and plasma prepared by centrifugation. Cerebrospinal fluid (CSF) was drawn from the cisterna magna using a 25 gauge needle attached to polyethylene tubing (2 mm) and a syringe. Brains were removed, rinsed with saline and weighed. All samples were immediately frozen on dry ice after processing and stored at −20°C until analysis. Brain samples were homogenized in four volumes of phosphate buffered saline (1 in 5 tissue dilution). Plasma, CSF and brain samples were analysed using a LC/MS-MS method. Calibration standard and quality control (QC) samples were prepared in untreated rat plasma or brain homogenate. The lower limit of quantitation (LLOQ) for all compounds was 0.1 ng ml^{-1} while the upper limit of quantitation (ULOQ) ranged from 25 to 100 ng ml^{-1}, depending on the dose received. Aliquots of plasma or brain (50 μl) were basified using 50 mM K_2HPO_4, pH 8.0 (200 μl) and mixed with internal standard (atropine, 10 μl of 50 ng ml^{-1}) before loading onto a 96-well solid phase extraction plate (Waters Oasis HLB, 10 mg). Following several washes (400-μl water, followed by 400-μl methanol : water 10:90), compounds were eluted using methanol (400 μl) and eluant dried under nitrogen heated to 40°C. Samples were reconstituted in 50-μl 5 mM ammonium acetate buffer containing 0.1% formic acid (v/v) before analysis by LC/MS-MS. Extracted samples (10 μl) were injected onto a Phenomenex Luna C18 analytical column (5 μM, 2.1 × 50 mm). The liquid chromatography system consisted of a gradient mixture of acetonitrile and 5 mM ammonium acetate pH adjusted with formic acid (0.1%,

v/v) maintained at a flow rate of 0.3 ml min^{-1}. Samples containing concentrations above the ULOQ were diluted with control matrix and re-analysed. CSF samples (20 µl) were mixed with internal standard and ammonium acetate buffer [5 mM with 0.1% formic acid (v/v)] and were quantified using a direct-inject method onto the LC/MS-MS system described above with standard curves prepared in untreated rat plasma ultrafiltrate. Data were acquired in positive ion mode with an ion spray probe voltage of 5.5 kV using the same reaction monitoring transitions as in the transcellular flux experiments, with the internal standard atropine monitored at m/z 290→124.

Plasma and brain binding

Binding of compounds to rat plasma or rat brain was determined by a previously described equilibrium dialysis method [20]. Briefly, untreated plasma or brain homogenate (5× diluted with PBS) was fortified with test compound to yield a final concentration of 1 µM. Samples were placed in a 96-well equilibrium dialysis block (HTDialysis, Gales Ferry, CT, USA) fitted with Spectra-Por 2 membranes (Spectrum Laboratories, Rancho Dominguez, CA, USA) and incubated at a temperature of 37°C, humidity of 95% and CO_2 concentration of 5%. After 6 h, aliquots (10 µl) of buffer and matrix were removed and added directly to a 96-well polypropylene block containing internal standard in acetonitrile (atropine, 50 ng ml^{-1}). An equal volume of the opposite matrix was added to each sample to yield uniform sample composition. All samples were analysed using LC/MS-MS with conditions similar to those described above. The unbound fraction in plasma (f_{up}) was calculated using the ratio of drug concentrations in buffer to matrix. Unbound fraction in brain (f_{ub}) was calculated in a similar fashion but tissue dilution factor (D) was taken into account according to the correction described by Kalvass & Maurer [20], whereby $f_{ub} = 1/D/[(1/f_{u2}) - 1] + 1/D$, where f_{u2} = unbound fraction measured in diluted tissue homogenate.

Analysis of in vivo *brain penetration data*

The treatment of data obtained from *in vivo* brain penetration studies has been discussed extensively in the literature and has underlined the value of applying knowledge of tissue binding in comparing tissue concentrations, and hence understanding brain penetration [19, 20, 25]. Furthermore, comparsion of results obtained using unbound brain tissue homogenate concentrations with *in vivo* microdialysis has supported the use of free concentrations in brain and CSF as surrogates for concentrations in brain interstitial fluid [26]. Therefore, the tissue concentration, plasma protein binding and brain binding data were used to calculate the following parameters:

$$\text{Brain : plasma ratio (B : P)} = \text{total concentration in brain (ng g}^{-1}\text{) : total concentration in plasma (ng ml}^{-1}\text{)}$$

$$\text{Unbound concentration in plasma} = \text{total concentration in plasma} \times f_{up}$$

$$\text{Unbound concentration in brain} = \text{total concentration in brain} \times f_{ub}$$

$$\text{Ratio of unbound fraction fractions in brain and plasma} = f_{ub} : f_{up}$$

$$\text{Kp,free} = \text{unbound concentration in brain : unbound concentration in plasma}$$

$$\text{CSF : free plasma ratio} = \text{concentration in CSF : unbound concentration in plasma}$$

Results

Physicochemical property assessment of OAB agents

The physicochemical properties that describe the lipophilicity, hydrogen bonding potential, polarity and flexibility of the range of antimuscarinics studied are summarized in Table 1. The compounds used for this investigation possess relatively low molecular weight (range 325–426 Da), typical of small drug molecules and, with the exception of trospium, can be classed as lipophilic based on their log D and calculated log P values (ranges log D 0.74–>3.3 and

Table 1

Physicochemical properties of various antimuscarinic agents

Antimuscarinic agent	Clog P	Log D	Hydrogen bond acceptors	Hydrogen bond donors	Rotatable bonds	Molecular weight (Da)	PSA (Å^2)
Trospium	–1.2	–1.22	3	1	5	393	46.5
5-HMT	3.7	0.74	3	2	8	341	43.7
Darifenacin	3.6	2.7	3	2	7	427	55.6
Solifenacin	4.7	1.69	3	0	4	362	32.8
Tolterodine	5.2	1.83	2	1	7	325	23.5
Oxybutynin	4.9	>3.3	3	1	8	357	49.8
Fesoterodine	4.4	ND	2	1	11	412	49.8

For definition of parameters in the table, refer to *Methods*.

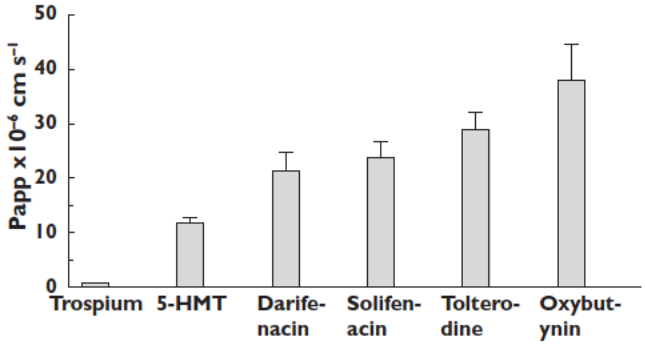

Figure 1

Passive transport of antimuscarinic agents in RRCK cells. Fluxes of compounds across RRCK cell monolayers in the apical to basolateral (A→B) direction are shown. Incubations were performed in triplicate and error bars represent SDs

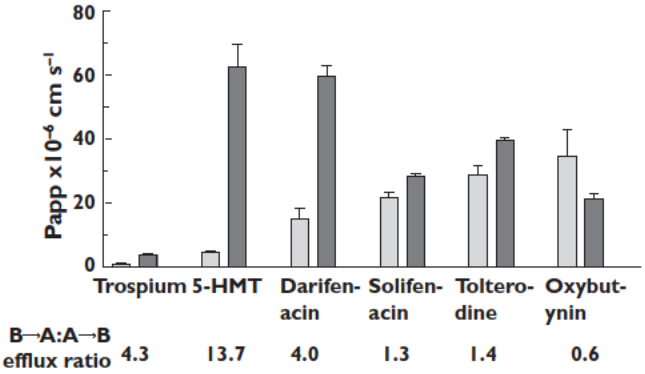

Figure 2

Transcellular flux of antimuscarinic agents in MDCK-MDR1 cells. Fluxes of compounds across MDCK-MDR1 cell monolayers were measured in apical to basolateral (A→B) and basolateral to apical (B→A) directions. The ratio of A→B/B→A fluxes (efflux ratio) is shown under each compound. Incubations were performed in triplicate and error bars represent SDs. A→B flux ( ); B→A ( )

clog P 3.6–4.9). The rank order of lipophilicity determined by log D [23] was oxybutynin > darifenacin > tolterodine ≈ solifenacin ≈ fesoterodine > 5HMT > trospium. Trospium (log D −1.22, clog P −1.2) is a much more hydrophilic compound in comparison due to the presence of a quaternary amine group that is ionized at physiological pH. Hydrogen bonding potential evaluated as the sum of hydrogen bond donors and acceptors was broadly similar between compounds, with rank order darifenacin = 5-HMT (5) > oxybutynin = trospium (4) > tolterodine = solifenacin = fesoterodine (3). All the compounds possessed relatively low PSA values ranging from 23.5Å^2 for tolterodine to 55.6 Å^2 for darifenacin. The number of rotatable bonds in a molecule is a measure of the flexibility of the compound. The range in the number of rotatable bonds in this series of compounds is relatively large with solifenacin having the lowest value (4) and 5-HMT and darifenacin having the highest value (8).

Transcellular flux across RRCK and MDR1-MDCK cell monolayers

In vitro cell membrane permeability and the influence of P-gp were assessed in cell lines designed to measure transcellular flux in the presence and absence of P-gp. A stable population of MDCK cells was selected by flow cytometry to have little or no functional P-gp that would contribute to efflux of substrates of this protein. In this cell line, designated RRCK, compounds displayed a range of flux values in the apical to basolateral direction (A→B) (Figure 1), and compounds could be classed as possessing low (<5 × 10^{-6} cm s^{-1}), moderate (5–15 × 10^{-6} cm s^{-1}) or high (>15 × 10^{-6} cm s^{-1}) transcellular flux. Thus, trospium (P_{app} = 0.63 × 10^{-6} cm s^{-1}) possessed low flux, 5-HMT moderate and solifenacin, tolterodine, darifenacin and oxybutynin high flux values.

The ability of compounds to act as P-gp substrates was assessed in MDCK cells transfected with the human mdr1 gene that expresses P-gp (MDCK-MDR-1). The ratio of apical to basolateral : basolateral to apical fluxes (A→B : B→A efflux ratio) was used as an index of P-gp-mediated efflux across MDCK-MDR-1 monolayers (Figure 2). The efflux ratios shown by the range of compounds varied between 0.6 and 13.7. Using an efflux ratio of >2 to indicate significant P-gp-mediated efflux [27], it was found that trospium, 5-HMT and darifenacin were likely to be substrates of the P-gp transporter, whereas solifenacin, tolterodine and oxybutynin were unlikely to act as substrates.

In vivo *CNS penetration of OAB agents in rats*

Determination of plasma, brain and CSF drug concentrations by specific LC/MS-MS afforded the required sensitivity and selectivity for accurate determination of drug concentration in tissues and ensured that metabolites did not contribute to apparent drug concentrations (the tissue concentration data used to determine brain penetration are shown in Table 2). CNS penetration was initially assessed by calculating the total brain : plasma concentration ratios (B : P) and CSF : free plasma concentration ratios (CSF : free plasma). During collection of the brain in these experiments, blood remains in the tissue and following homogenization and LC/MS-MS analysis the residual blood can contribute an observed B : P of up to 0.04, reflecting presence of drug in the vasculature of the brain rather than true brain penetration [28]. Hence, values of B : P below 0.04 and CSF : free plasma approaching 0 are consistent with no significant brain penetration and no equilibrium between CSF and free plasma. The results of CNS penetration *in vivo* are summarized in Table 3 and displayed graphically in increasing order of their CNS penetration in Figure 3.

In parallel experiments, scopolamine (0.3 mg kg^{-1}) and N-methylscopolamine (0.3 mg kg^{-1}) were administered as

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