Cardiac effects of muscarinic receptor antagonists used for voiding dysfunction

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Antimuscarinic agents are the main drugs used to treat patients with the overactive bladder (OAB) syndrome, defined as urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia. Since the treatment is not curative and since OAB is a chronic disease, treatment may be life-long. Antimuscarinics are generally considered to be 'safe' drugs, but among the more serious concerns related to their use is the risk of cardiac adverse effects, particularly increases in heart rate (HR) and QT prolongation and induction of polymorphic ventricular tachycardia (torsade de pointes). An elevated resting HR has been linked to overall increased morbidity and mortality, particularly in patients with cardiovascular diseases. QT prolongation and its consequences are not related to blockade of muscarinic receptors, but rather linked to inhibition of the hERG potassium channel in the heart. However, experience with terodiline, an antimuscarinic drug causing torsade de pointes in patients, has placed the whole drug class under scrutiny. The potential of the different antimuscarinic agents to increase HR and/or prolong the QT time has not been extensively explored for all agents in clinical use. Differences between drugs cannot be excluded, but risk assessments based on available evidence are not possible.

Introduction

It is text-book knowledge that 'classical' antimuscarinics, i.e. atropine and drugs with a similar receptor blocking profile, have the ability to increase heart rate (HR). Antimuscarinic agents are the main drugs used to treat patients with the overactive bladder (OAB) syndrome, defined as urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia [1]. The treatment of OAB with antimuscarinics is not curative and since OAB is a chronic disease, treatment may be life-long. Since many epidemiological studies have suggested an association between an increased resting HR and overall morbidity and mortality in patients, particularly in patients with cardiovascular disease [2–9], there is a concern that antimuscarinics used for treatment of OAB can cause increases in HR that may be harmful. Another concern is whether or not these drugs have a potential risk of producing QT interval changes.

As both OAB and cardiovascular disease increase with age, many patients with OAB will have concomitant cardiovascular disorders. The prevalence of cardiovascular co-morbidities was shown to be significantly higher in patients with than without OAB, and previous exposure to medications with antimuscarinic effects was also higher in

patients with OAB [10]. Antimuscarinic-induced increases in HR may potentially put these patients at increased risk. However, increases in HR have, as a rule, not been reported as a major adverse effect in OAB studies of antimuscarinics, and use of these drugs did not seem to increase the risks of ventricular arrhythmias and sudden death in older patients, as assessed in a retrospective database study [11].

The single most common cause of the withdrawal or restriction of the use of drugs that have been marketed has been QT interval prolongation with the risk of life-threatening polymorphic ventricular tachycardia [12]. Antimuscarinics are generally considered 'safe', but negative experience with terodiline causing polymorphic ventricular tachycardia (torsade de pointes) [13], has focused interest specifically on potential cardiovascular adverse effects for the whole drug class. Although terodiline is not a 'pure' antimuscarinic but classified as an antimuscarinic with calcium antagonistic properties, QT prolongation and torsade de pointes have been a main concern when introducing new antimuscarinics [14]. However, QT prolongation is considered to be a specific drug effect, linked to inhibition of the hERG potassium channel in the heart [15], and not to effects mediated via muscarinic receptors.

In the present review, the basis for the different antimuscarinics' effects on cardiac function, and clinical

experience with the drugs are briefly discussed with special reference to effects on heart rate and on QT time.

Parasympathetic innervation of the heart

The peripheral autonomic nervous system provides the heart with parasympathetic as well as sympathetic innervation. The parasympathetic nervous system originates from medial medullary sites (nucleus ambiguus, nucleus tractus solitarius and dorsal motor nucleus) and is modulated by the hypothalamus. The vagus nerve carries the fibres to the heart through vagal efferents extending from the medulla to postganglionic nerves that innervate the atria via ganglia located in cardiac fat pads [16]. All parts of the mammalian heart are innervated by parasympathetic nerves, although the supraventricular tissues are more densely innervated than the ventricles [17, 18]. Postganglionic parasympathetic and sympathetic nerves may interact to affect cardiac muscarinic receptors [19]. Vagus nerve afferent activation, originating peripherally, can modulate efferent sympathetic and parasympathetic function centrally and at the level of the baroreceptor. Efferent vagus nerve activation can have tonic and basal effects that inhibit sympathetic activation and release of norepinephrine at the presynaptic level. The right vagus nerve provides innervation to the sinoatrial (SA) node region. Parasympathetic activation can affect atrioventricular (AV) nodal conduction mediated predominantly through the left vagus nerve.

Indicators of vagal activity

Normally, the activity of the sympathetic and parasympathetic systems is in a dynamic balance. There is a well-documented circadian rhythm such that sympathetic activity is higher during daytime hours and parasympathetic activity increases at night [20].

There are several approaches commonly used to assess parasympathetic influences on heart rate [20, 21] including measurements of (i) resting HR and the HR response to pharmacological blockade of muscarinic cholinergic receptors ('cardiovagal tone'), (ii) the rapid decline (recovery) of HR after termination of exercise (parasympathetic reactivation), (iii) the HR variability (HRV) attributed to parasympathetic modulation and (iv) reflex changes in HR elicited by activation or inhibition of specific sensory nerves (e.g. baroreflex sensitivity assessments).

Resting HR is under tonic inhibitory control via the vagus and is considered a simple, inexpensive and noninvasive measure of vagal function [20, 21]. HR can be used as a rough indicator of autonomic balance. Acetylcholine released from post-ganglionic cardiac parasympathetic

nerves reduces HR by binding to muscarinic cholinergic receptors (primarily M_2 subtype) on SA nodal cells (see below). Thus, the level of ongoing tonic parasympathetic activity can be estimated by measuring the increase in HR that occurs in response to acute administration of classical non-selective receptor subtype antimuscarinics such as methylatropine. The mean change in HR reflects the parasympathetic (vagal) tone.

Several studies have shown a positive relationship between resting HR and all-cause and cardiovascular mortality [22]. Greenland *et al.* performed a prospective cohort study including 33 781 participants aged 18–74 years followed over 22 years to determine the association between resting HR and cardiovascular mortality. They found that a 12 beats min^{-1} higher resting HR increases the relative risk of fatal coronary disease for men of all ages and for women aged over 40 years. They also demonstrated an increased risk of death from all causes with higher HR in five of six age/sex groups [3]. In patients with coronary artery disease and left-ventricular systolic dysfunction, Fox *et al.* found that elevated HR (70 beats min^{-1} or greater) identified those at increased risk of cardiovascular outcomes [7]. Hsia *et al.*, investigating resting HR as an independent predictor of cardiovascular risk in 129 135 postmenopausal women, found that resting HR independently predicted myocardial infarction or coronary death, but not stroke [8]. It is still unclear whether the HR has a direct effect on adverse outcomes or whether the responsible aetiology is an underlying autonomic imbalance [22, 23].

The change in HR following cessation of exercise is another measure that has been used to characterize vagal function [24]. The decrease in HR after termination of exercise has been termed HR recovery and standardized methods have been developed for its assessment. Various HR variables tested for prediction of mortality have given conflicting results [25, 26]. However, HR recovery in the immediate post-exercise phase seems to be the most reliable predictor [27].

Jouven *et al.* studied a total of 5713 asymptomatic working men aged 42–53 years without clinically detectable cardiovascular disease. The participants underwent standardized graded exercise testing between 1967 and 1972. Jouven *et al.* recorded the subjects' resting HR, the increase in rate from the resting level to the peak exercise level, and the decrease in rate from the peak exercise level to the level 1 min after the termination of exercise. They found that a resting HR over 75 beats min^{-1} , a HR during exercise lower than 89 beats min^{-1} and a decrease in HR less than 25 beats min^{-1} after exercise cessation was associated with an increased risk of sudden cardiac death, a moderate but significantly increased risk of death from any cause, but not of non-sudden death from myocardial infarction [28].

Parasympathetic reactivation after exercise can be effectively inhibited by non-subtype selective antimuscarinics such as atropine [24].

HRV in both time and frequency domains has been used successfully as a measure of vagal activity [20, 21, 29, 30]. In the time domain, the standard deviation of the interbeat intervals, the percentage of interbeat intervals differences greater than 50 ms and the mean square of the successive differences in interbeat intervals have been shown to be useful indices of vagal activity. In the frequency domain, both low frequency (0.04–0.15 Hz) and high frequency (0.15–0.40 Hz) spectral power have been used. Whereas there is little contention concerning high frequency power reflecting primarily parasympathetic influences, low frequency power has been shown to reflect both sympathetic and parasympathetic influences. Subtype non-selective antimuscarinics were shown to effectively decrease the high frequency power [31–33].

A single dose of 8 mg tolterodine ER, but not 4 mg seemed to reduce resting HRV vs. placebo in young healthy subjects [34]. This observation might be particularly relevant for patients with pre-existing cardiac conditions on daily OAB treatment.

Baroreflex sensitivity (BRS) is an index of the responsiveness of the cardiovascular system to changes in blood pressure. The arterial baroreflex buffers abrupt changes in blood pressure: increased arterial pressure activates arterial baroreceptors, leading to augmented parasympathetic cardiac outflow and decreased HR. BRS is considered a useful indicator of vagal function [20, 21], and has been applied to the dynamic assessment of cardiac antimuscarinic drug effects in humans [32].

The literature linking a decrease in BRS to morbidity and mortality is extensive [35–37]. These studies suggest that low values of BRS are associated prospectively with death and disability.

Cardiac muscarinic receptors

Release of acetylcholine from postganglionic parasympathetic nerve terminals activates muscarinic receptors in the heart. Muscarinic receptors can be found not only in the SA and AV nodes, but also in the endocardium, epicardium, T-tubules of cardiomyocytes, right and left atrium, ventricular myocytes and coronary arteries including small vessels [38–40]. Stimulation of muscarinic receptors within the heart, specifically the M_2 subtype, modulates pacemaker activity and AV conduction, and directly (in atria) or indirectly (in ventricles) the force of contraction [38, 39, 41].

Mice lacking muscarinic receptors have been used for investigating the role of muscarinic receptor subtypes in regulating HR. Available evidence from such mice suggests that only the M_2 -receptors are responsible for heart rate regulation [42–45].

Details are still emerging of the functional roles of other muscarinic receptor subtypes that have also been

localized in the heart (M_1 , M_3 and M_5). Functional M_1 -receptors, which increase heart rate, have been reported in animal cardiac tissue [46, 47] and human atrial myocytes [39, 48]. However, the basal heart function of mice lacking M_1 -receptors was unchanged compared with wild type. M_1 -receptors were shown to influence cardiac activity by stimulating catecholamine release from sympathetic neurons [49]. On the other hand, functional M_1 receptors increasing heart rate (assessed by pirenzepine administration) have been demonstrated in humans *in vivo* [50–52], and may play a role in the paradoxical heart rate lowering with low doses of muscarinic receptor antagonists [53]. It was suggested that pirenzepine decreased heart rate via inhibition of presynaptic M_1 autoreceptors, thereby releasing endogenous acetylcholine. Functional M_3 -receptors have been identified in animal cardiac tissue [39, 41, 54, 55] and in human atrial tissue [48, 56]. However, data obtained using knockout mice suggest limited involvement of M_3 -receptors in physiological cardiac function.

To date, it does not appear that muscarinic receptor subtypes other than M_2 -receptors mediate significant effects on HR. It is, however important to consider that the role of muscarinic receptor subtypes in modulating cardiac function might alter in pathological conditions. An increased M_3 -receptor density, but a decrease in M_2 -receptors, has been reported in chronic atrial fibrillation and experimental congestive heart failure [39].

The genes for M_2 and M_3 -receptors are expressed in human coronary arteries [57], although the functional importance of these receptors is currently unclear. The principal effect of muscarinic receptor stimulation in the human coronary vasculature is vasodilation by nitric oxide release from functional endothelium [58]. On the other hand, if there is no functional endothelium present, the smooth muscle effect of cholinergic stimulation becomes unmasked and vasoconstriction can be observed. Thus, intracoronary cholinergic agonist injection during coronary angiography can be used for identification of areas with endothelial dysfunction [59].

Variations in autonomic tone have been proposed to play a role in the induction of epicardial spasm in patients with variant angina. Thus, Choi *et al.* suggested that vagal stimulation might precipitate coronary spasm through the action of acetylcholine. Acetylcholine is released at the medial-adventitial border, causing vasoconstriction by coming in contact first with vascular smooth muscle [60]. Studies using knockout mice lacking M_2 , M_3 or M_5 -receptors have suggested that M_3 -receptors predominantly mediate acetylcholine-induced (endothelium-dependent) dilatation of mouse coronary arteries [61]. However, it may be speculated that the vasospastic effect of acetylcholine on coronary artery smooth muscle is mediated by M_3 -receptors. Whether or not antimuscarinic drugs have any direct effect on coronary vessels in patients is not known.

Cardiac electrophysiology

Voltage-dependent ion channels control the electrical activity of the heart. During the heartbeat, the influx of Na^+ and Ca^{2+} , through their respective channels, serves to depolarize the myocardium, whereas K^+ efflux through K^+ channels repolarizes the heart. These channels give rise to the shape and the duration of the action potential on the cellular level and to the electrocardiogram (ECG) waveform measured clinically. Any alteration in the activity of these channels can lead to changes in the ECG wave form and potentially to the development of cardiac arrhythmia. One such proarrhythmic condition is drug-induced (or acquired) long QT syndrome where administration of a drug slows cardiac repolarization, resulting in a prolongation of the QT interval on the electrocardiogram [12, 62]. This QT prolongation may be associated with the development of the ventricular arrhythmia known as torsade de pointes. It is now believed that most cases of acquired QT prolongation are due to specific inhibition of the human cardiac K^+ channel known as human ether-a-go-go related gene (hERG). The hERG channel carries the rapid component of the delayed rectifier K^+ current in the human heart (IKr). hERG channel inhibition is considered to be the mechanism that underlies the QT prolongation and ventricular arrhythmias associated with the administration of drugs [62].

The SA node normally serves as the pacemaker of the heart. Spontaneous action potentials in SA nodal cells possess several significant characteristics. When compared with the action potentials of atrial or ventricular cardiomyocytes, the SA nodal cell action potential is characterized by a pacemaker potential, seen as a slow depolarization during phase 4 diastole. The intrinsic HR is modulated by the parasympathetic (slowing the rate) and sympathetic (increasing the rate) nervous input. The rate of the denervated heart is higher than that of the normal resting HR, as the resting HR is highly dependent on the degree of parasympathetic tone.

Cardiac effects of antimuscarinics

Currently, darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine and trospium are the major antimuscarinic drugs that are employed for the treatment of OAB. These molecules differ in their pharmacological profile at the five human recombinant muscarinic receptors [63] and in their pharmacokinetics [64]. Tolterodine (including its 5-hydroxymethyl metabolite), fesoterodine, propiverine and trospium essentially do not discriminate between the five subtypes. Oxybutynin (and its N-desethyl metabolite) and solifenacin do possess marginal selectivity (<10-fold) for M_3 over the M_2/M_5 subtypes, but do not distinguish between M_3 and M_1/M_4 subtypes. In contrast,

darifenacin has a high degree of selectivity for M_3 over the M_2/M_4 subtypes and modest selectivity for M_3 over the M_1/M_5 subtypes.

The published amount of both preclinical and clinical information on cardiac effects of antimuscarinics used in OAB treatment varies between drugs. Some information is accessible only via the prescribing information on the different drugs. With the lack of published comparative studies, assessment of whether or not one drug has a greater risk of producing adverse effects than another is not possible.

Differentiating risk profiles based on pharmacokinetics, receptor selectivity and clinical effects would be beneficial to physicians in choosing an individually optimum therapy. However, there are few clinical trials designed to assess the cardiovascular effects of antimuscarinics and a very limited number of head-to-head comparisons of the drugs. With age, a decrease in the expression of cardiac muscarinic receptors and a reduction in the HR response to antimuscarinics (increase) have been demonstrated [65]. In addition, as mentioned previously, the M_1 receptor antagonist pirenzepine in low doses decreases resting heart rate. This effect also declines with age [50]. However, whether or not the cardiovascular responses to antimuscarinics decrease in older patients with OAB and/or in patients with cardiac co-morbidities is not known.

Darifenacin

The pharmacological receptor profile of darifenacin, showing selectivity for M_3 receptors, suggests that its propensity to increase heart rate should be low. Indeed, this seems to be the case in both dogs [66, 67] and humans [68, 69]. In a prospective, three-way crossover, randomized, double-blind study, Olshansky *et al.* assessed the HR effects of 7 days' exposure to tolterodine (4 mg day^{-1}), darifenacin (15 mg day^{-1}) and placebo in 162 healthy participants > or = 50 years. Heart rate was measured by 24 h Holter monitoring. It was found that tolterodine significantly increased HR vs. darifenacin ($+1.84 \text{ beats min}^{-1}$) and HR vs. placebo ($+1.42 \text{ beats min}^{-1}$), while darifenacin did not affect HR vs. placebo. Interestingly, the proportion of participants with an increase in mean HR per 24 h of > or = 5 beats min^{-1} was higher with tolterodine than with darifenacin ($P = 0.0004$) or with placebo ($P = 0.0114$), but did not differ between darifenacin and placebo [68]. These results were confirmed in another study of similar design [69].

To assess possible effects of QT intervals, the effect of 6 day treatment of 15 mg and 75 mg darifenacin on QT/QT_c interval was evaluated in a multiple dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel-arm design study in 179 healthy adults (44% male, 56% female) aged 18 to 65 years. Subjects included 18% poor metabolizers and 82% extensive metabolizers. The QT interval was measured over a 24 h period both predosing and at steady state. The 75 mg darifenacin dose was chosen because this achieves expo-

sure similar to that observed in CYP2D6 poor metabolizers administered the highest recommended dose (15 mg) of darifenacin in the presence of a potent CYP3A4 inhibitor. At the doses studied, darifenacin did not result in QT/QT_c interval prolongation at any time during steady state, while moxifloxacin treatment resulted in a mean increase from baseline QT_c of about 7.0 ms when compared with placebo. In this study, darifenacin 15 mg and 75 mg doses demonstrated a mean HR change of 3.1 and 1.3 beats min⁻¹, respectively, when compared with placebo [70]. However, in the phase II/III clinical studies, the change in median HR following treatment with darifenacin was no different from placebo [71].

Kay *et al.* examined the pharmacodynamics of 7.5 and 15 mg of darifenacin in healthy males compared with dicyclomine and placebo. The study was powered to observe differences in cognitive function tests only. Darifenacin did not affect the HR or HRV at 4 h after the dose compared with placebo. However, dicyclomine reduced the HR by 4.8 beats min⁻¹ and increased the HRV by 11.9% compared with placebo [72].

Fesoterodine

Fesoterodine is a prodrug that is promptly and completely converted via nonspecific esterases to its active metabolite, 5-hydroxymethyltolterodine (5-HMT). It is this metabolite that functions as a competitive muscarinic receptor antagonist. 5-HMT is chemically identical to the major active metabolite of tolterodine [73–75].

Fesoterodine was found to cause dose-related increases in HR. When compared with placebo in a study of potential QT effects (see below), the mean increase in HR associated with doses of 4 mg day⁻¹ and 28 mg day⁻¹ was 3 beats min⁻¹ and 11 beats min⁻¹, respectively. In two phase III placebo-controlled studies in patients with OAB, the mean increase in HR compared with placebo was approximately 3–4 beats min⁻¹ after 4 mg day⁻¹ and 3–5 beats min⁻¹ after 8 mg day⁻¹ [76]. A study evaluating the efficacy, safety and tolerability of fesoterodine for OAB randomized patients to placebo, fesoterodine 4 mg or fesoterodine 8 mg. One cardiac adverse event of atrial fibrillation was reported in the placebo group. The mean change in HR for placebo, 4 and 8 mg fesoterodine was 1, 3 and 4 beats min⁻¹, respectively. The percent of patients with a corrected QT interval (Fridericia's formula) of over 450 ms, or a change from baseline of more than 30 ms was similar in the placebo and both treatment groups [77].

The effects of fesoterodine 4 mg and 28 mg on the QT interval were evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400 mg once a day) parallel trial with once daily treatment over a period of 3 days in 261 male and female subjects aged 44 to 65 years. ECG parameters were measured over a 24 h period at pre-dose, after the first administration and after the third administration of study medication. Fesoterodine 28 mg was chosen because this dose, when administered

to CYP2D6 extensive metabolizers, results in an exposure to the active metabolite that is similar to the exposure in a CYP2D6 poor metabolizer receiving fesoterodine 8 mg together with CYP3A4 blockade. Corrected QT intervals (QT_c) were calculated using Fridericia's correction and a linear individual correction method. Analyses of 24 h average QT_c, time-matched baseline-corrected QT_c and time-matched placebo subtracted QT_c intervals indicated that fesoterodine at doses of 4 and 28 mg day⁻¹ did not prolong the QT interval. The sensitivity of the study was confirmed by positive QT_c prolongation by moxifloxacin [78].

Oxybutynin

Jones *et al.* investigated the cardioactive properties of oxybutynin in guinea pig and rabbit cardiac tissue. Recordings of membrane currents from whole-cell-configured ventricular myocytes showed action potentials from guinea pig and rabbit papillary muscles. L-type Ca²⁺ current [I(Ca)_L], inward-rectifier K⁺ current [I(K₁)], and delayed-rectifier K⁺ current [I(K)] were unaffected by < or = 1 μM oxybutynin, and inhibited by higher concentrations. Because the peak therapeutic plasma concentrations of oxybutynin are in the 0.01–0.1 μM range, the investigators concluded that it was highly unlikely that oxybutynin would have adverse effects on cardiac electrical activity [79].

Abrams *et al.* compared the efficacy, safety and tolerability of oxybutynin and propiverine in a randomized crossover study. HR and HRV were monitored with ECG recordings on a Holter monitor at baseline and at the end of the treatment period. The patients on propiverine 20 mg daily and propiverine 15 mg three times a day regimens had a statistically significant increased HR and decreased HRV. Patients on oxybutynin had similar HR and HRV compared with placebo [80]. Chapple & Abrams performed a randomized double-blinded crossover (*n* = 65) study with three treatment cohorts: darifenacin (immediate release) 2.5 mg three times a day or oxybutynin 5 mg three times a day, darifenacin controlled release (CR) 15 mg once a day or oxybutynin 5 mg three times a day, and darifenacin CR 30 mg or oxybutynin 5 mg three times a day. There were no significant HR differences between baseline and treatment groups. However, there was greater HRV in the oxybutynin group for the first and second cohort [81].

The information on possible QT effects of oxybutynin in patients is scarce and specific studies seem to be lacking. The drug did not cause changes in the ECG of elderly patients with urinary incontinence [82].

Propiverine

Christ *et al.* investigated the effects of propiverine on cardiac ion channels and action potentials as well as on contractile properties of cardiac tissue. The drug blocked hERG channels expressed in HEK293 cells, in a concentration-dependent manner, as well as the native I_{Kr}

current in guinea pig ventricular myocytes. In guinea-pig ventricular and human atrial myocytes, propiverine also blocked $I_{Ca,L}$ and reduced the force of contraction. Despite block of I_{Kr} , action potential duration was not prolonged in guinea-pig and human ventricular tissue, but decreased progressively until excitation failed altogether. The authors concluded that their study did not provide evidence for an enhanced cardiovascular safety risk for propiverine. They suggested that lack of torsadogenic risk of propiverine is related to enhancement of repolarization reserve by block of $I_{Ca,L}$ [83].

In a double-blind, multicentre, placebo-controlled, randomized study, Dorschner *et al.* investigated the efficacy and cardiac safety of propiverine in 98 elderly patients (21 male, 77 female; 67.7 ± 6.3 years) suffering from urgency, urgency incontinence or mixed urgency-stress incontinence. After a 2-week placebo run-in period, the patients received propiverine (15 mg three times daily) or placebo (three times daily) for 4 weeks. Before and during the treatment period, standard ECGs and 24 h long-term ECGs were recorded. Resting and ambulatory ECGs indicated no significant changes. Neither the frequency-corrected QT interval nor other cardiac parameters were relevantly altered. The frequency of cardiac events was random, revealing no difference between placebo and propiverine [84].

A previously mentioned cross-over study comparing oxybutynin, placebo and propiverine 20 mg daily and 15 mg three times a day found a significantly higher HR and decreased HRV in both propiverine treatment groups [80].

Solifenacin

Michel *et al.* reported the results of an open-label, post-marketing surveillance study, specifically designed to evaluate the cardiovascular safety of solifenacin 5–10 mg once daily during a 12-week treatment course. There were no specific inclusion or exclusion criteria, but they systematically documented HR-relevant co-morbidities and co-medications. The study was conducted in 4450 patients with OAB under the care of office-based urologists. They found no clinically relevant alterations in HR which was the primary outcome measurement (75.2 ± 8.2 beats min^{-1} pre-treatment vs. 74.5 ± 7.6 beats min^{-1} at study end). In the subgroup of patients who underwent ECG both before and during treatment, no increase in the prevalence of pathological findings was noted [85].

The effect of 10 mg and 30 mg solifenacin on the QT interval was evaluated at the time of peak plasma concentration of solifenacin in a multi-dose, randomized, double-blind, placebo and positive-controlled (moxifloxacin 400 mg) trial. Subjects were randomized to one of two treatment groups after receiving placebo and moxifloxacin sequentially. One group ($n = 51$) went on to complete three additional sequential periods of dosing with solifenacin 10, 20, and 30 mg while the second group ($n = 25$) in

parallel completed a sequence of placebo and moxifloxacin. Study subjects were female volunteers aged 19 to 79 years. The 30 mg dose of solifenacin (three times the highest recommended dose) was chosen for use in this study because this dose results in a solifenacin exposure that covers those observed upon co-administration of 10 mg solifenacin with potent CYP3A4 inhibitors (e.g. ketoconazole 400 mg). Due to the sequential dose escalating nature of the study, baseline ECG measurements were separated from the final QT assessment (of the 30 mg dose level) by 33 days. The median difference from baseline HR associated with the 10 and 30 mg doses of solifenacin succinate compared with placebo was -2 and 0 beats min^{-1} , respectively. Because a significant period effect on QT_c was observed, the QT_c effects were analyzed utilizing the parallel placebo control arm rather than the pre-specified intra-patient analysis. Moxifloxacin was included as a positive control. The QT interval prolonging effect appeared greater for the 30 mg compared with the 10 mg dose of solifenacin. Although the effect of the highest solifenacin dose studied (three times the maximum therapeutic dose) did not appear as large as that of the positive control moxifloxacin at its therapeutic dose, the confidence intervals overlapped. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels [86].

In association with solifenacin use in worldwide post-marketing experience, QT prolongation and torsade de pointes have been reported [86]. However, the frequency of events and the role of solifenacin in their causation cannot be reliably determined. QT prolongation and torsade de pointes associated with solifenacin in an 81-year old woman was reported by Asajima *et al.* [87].

Tolterodine

Kang *et al.* studied the effects of tolterodine on cardiac ion channels and action potential recordings. Using patch-clamp electrophysiology, they found that tolterodine was a potent antagonist of the hERG K^+ channel, displaying an IC_{50} value of 17 nM. This potency was similar to that observed for the antiarrhythmic drug dofetilide (IC_{50} of 11 nM). The tolterodine block of hERG displayed positive voltage dependence, suggesting an interaction with an activated state. Tolterodine had little effect on the human cardiac Na^+ channel at concentrations of up to 1 μM . Inhibition of L-type Ca^{2+} currents by tolterodine was frequency-dependent with IC_{50} values measuring 143 and 1084 nM at 1 and 0.1 Hz, respectively. Both tolterodine and dofetilide prolonged action potential duration in single guinea pig myocytes over the concentration range of 3 to 100 nM. However, prolongation was significantly larger for dofetilide compared with tolterodine. The authors concluded that tolterodine seems to be unusual in that it blocks hERG channels with high affinity, but produces little QT prolongation clinically. They suggested that the low plasma concentrations after therapeutic doses combined

with mixed ion channel effects, most notably Ca^{2+} channel blockade, may serve to attenuate the QT prolonging effects of this potent hERG channel antagonist [88].

Martin *et al.* assessed differences in the electrophysiologic actions of terodiline and tolterodine on hERG channel current (HEK cells) and cardiac Purkinje fibre repolarization. The IC_{50} for hERG channel block (37°C) by tolterodine was 9.6 nM and by terodiline was 375 nM, values near or below clinical concentrations. Tolterodine elicited concentration-dependent prolongation of the action potential duration (APD90). In contrast, terodiline depressed the action potential plateau and induced triangulation without affecting APD90. The triangulation ratios (normalized ratio of APD50 over APD90) for terodiline were 0.94 and 0.59 for 1.0 and 10 mM and for tolterodine, were 0.99 and 0.97 at 7 and 70 nM. The authors concluded that tolterodine, despite being a potent hERG channel blocker, had a benign clinical cardiac profile at therapeutic concentrations that may be due to its lack of triangulation, as well as extensive plasma protein binding. However, preclinical data predicted risk of QT prolongation at supratherapeutic concentrations [89].

Clinically, the effect of 2 mg twice a day and 4 mg twice daily of tolterodine immediate release (IR) tablets on the QT interval was evaluated in a four-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg once daily) study in healthy male ($n = 25$) and female ($n = 23$) volunteers aged 18–55 years. Study subjects (approximately equal representation of CYP2D6 extensive metabolizers and poor metabolizers) completed sequential 4-day periods of dosing with moxifloxacin 400 mg once daily, tolterodine 2 mg twice daily, tolterodine 4 mg twice daily and placebo. The 4 mg twice daily dose of tolterodine IR (two times the highest recommended dose) was chosen because this dose results in tolterodine exposure similar to that observed upon co-administration of tolterodine 2 mg twice daily with potent CYP3A4 inhibitors in patients who are CYP2D6 poor metabolizers. QT interval was measured over a 12 h period following dosing, including the time of peak plasma concentration of tolterodine and at steady state (Day 4 of dosing). Both Fridericia's (QT_cF) and a population-specific (QT_cP) method were used to correct QT interval for HR. The mean increase of HR associated with a 4 mg day^{-1} dose of tolterodine was 2.0 beats min^{-1} and with 8 mg day^{-1} 6.3 beats min^{-1} . The change in HR with moxifloxacin was 0.5 beats min^{-1} . The QT effect of tolterodine IR tablets appeared greater for 8 mg day^{-1} (two times the therapeutic dose) compared with 4 mg day^{-1} . The effect of tolterodine 8 mg day^{-1} was not as large as that observed after 4 days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped. The effect of tolterodine on QT interval was found to correlate with plasma concentration of tolterodine. There appeared to be a greater QT_c interval increase in CYP2D6 poor metabolizers than in CYP2D6 extensive metabolizers after

tolterodine treatment. The study was not designed to make direct statistical comparisons between drugs or dose levels [90].

Schiffers *et al.* studied the effect of tolterodine extended release (ER) 4 and 8 mg on HRV in healthy subjects. Resting HR increased (4 mg 60–68 beats min^{-1} ; 8 mg 63–73 beats min^{-1}) in both treatment groups. They found that a single dose of 8 mg tolterodine ER reduced HRV vs. placebo [34]. A study by Brynne *et al.* found a dose-related increase in HR, with an increase of +30% (19 beats min^{-1}) of the pre-dose value after 12.8 mg of tolterodine IR administration in 17 healthy male volunteers [91].

In a previously mentioned three-way crossover, randomized, double-blind study, Olshansky *et al.* assessed the HR effects of 7 days' exposure to tolterodine (4 mg day^{-1}), darifenacin (15 mg day^{-1}), and placebo in 162 healthy participants. HR was measured by 24 h Holter monitoring. It was found that, for tolterodine, the maximum increase in HR occurred at times close to the maximum plasma concentration and amounted to approximately 4 beats min^{-1} [68].

According to the prescribing information, there has been no association of torsade de pointes in the international post-marketing experience with tolterodine. Tachycardia, palpitations and peripheral oedema have been observed [92].

Trospium

Treatment with trospium may be associated with an increase in HR that correlates with increasing doses: 20, 40, 80, 120, 180, 240 and 360 mg. Increases in pulse rate (approximately 10–15 beats min^{-1} with the highest doses) appeared at 4 to 8 h and disappeared by 12 h post-dosing. No significant effect on blood pressure was noted at any dose. No ECG effects occurred at any dose except a 10 to 40 ms reduction in the QT interval due to the tachycardia [93]. In a study of the possible QT effects of the drug (see below), trospium caused, compared with placebo, a mean increase in HR of 9.1 beats min^{-1} for the 20 mg dose and 18.0 beats min^{-1} for the 100 mg dose [94]. In two U.S. placebo-controlled trials in patients with OAB, the mean increase in HR compared with placebo in one study was observed to be 3.0 and in the other 4.0 beats min^{-1} [95, 96].

The effect of trospium chloride on QT interval was evaluated in a single-blind, randomized, placebo- and active (moxifloxacin)-controlled trial in 170 healthy volunteers. Subjects were randomized to 5 days of placebo, moxifloxacin 400 mg once daily, or various doses of trospium chloride (ranging from 20 to 100 mg twice daily). The QT interval was evaluated over a 24 h period at steady state. The QT interval was not affected by any dose of trospium chloride while moxifloxacin had the expected effect of prolonging the mean Fridericia-corrected QT interval by 6.4 ms [94].

Conclusions

Among the more serious concerns related to the antimuscarinics used in the treatment of OAB are the risk of cardiac adverse effects, particularly increases in HR, QT interval prolongation and induction of polymorphic ventricular tachycardia (torsade de pointes). However, the potential of the different agents to increase HR or to prolong the QT interval has not been extensively explored. Based on available information, it cannot be excluded that some of the drugs can increase HR. However, such effects appear to be modest and their clinical relevance is not known. Specifically, careful studies in elderly patients and in patients with cardiovascular disease are desirable. Since thorough QT studies have not been performed with all drugs, increased risks with some of them cannot be excluded, as QT prolongation is related to the chemical structure of the individual agent and is not a class effect.

In general the cardiovascular safety of antimuscarinic drugs seems to be good. Differences between the drugs (in, for example, effects on HR) cannot be excluded, but risk assessments based on available evidence are not possible.

Competing Interests

K-E. Andersson: Consultancy for Allergan, Astellas, Novartis, Pfizer. L. Campeau: None. B. Olshansky: Consultancy for Novartis.

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