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Retrospective Analysis of the Safety Profile of Oral Moxifloxacin in Elderly Patients Enrolled in Clinical Trials

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Abstract

Background and objective: As aging is associated with physiological changes, including renal and hepatic insufficiency, and a higher risk of drug interactions, special attention needs to be directed towards the safety of medications in the elderly. The objective of this analysis was to evaluate the safety of oral moxifloxacin in elderly patients who were enrolled in clinical trials and to compare these results to those of other commonly used antibacterials.

Methods: Safety data from 27 prospective, randomised, comparative phase II/III trials of oral moxifloxacin included in the Bayer clinical trial database were pooled and analysed by age group (<65 years of age, 65–74 years of age, ≥75 years of age) and by treatment group (moxifloxacin vs comparator). The primary endpoints included rates of treatment-emergent adverse events (all adverse events regardless of causality), drug-related adverse events, drug-related serious adverse events, deaths and premature discontinuations because of a treatment-emergent adverse event. A treatment by age group interaction test was used to determine if the comparison between moxifloxacin and the comparator group in the incidence rates of any treatment-emergent or drug-related adverse events were affected by increasing age.

Results: Of the 12 231 patients who had valid safety data, 6270 had been treated with oral moxifloxacin and 5961 with a comparator antibacterial. The most frequently used comparators were cefuroxime and clarithromycin. Most patients (n = 9671) were <65 years of age (4939 moxifloxacin, 4732 comparator); 1636 patients were 65–74 years of age (842 moxifloxacin, 794 comparator); and 924 patients were ≥75 years of age (489 moxifloxacin, 435 comparator). The treatment by age group interaction test revealed that the comparison of drug-related adverse event rates between the moxifloxacin and comparator group were not affected by increasing age ($p = 0.43$). Rates of premature termination between the moxifloxacin and comparator treatment groups also did not increase with age ($p = 0.552$). No arrhythmias related to corrected QT (QTc) interval prolongation were reported following oral moxifloxacin or comparator treatment in this large group of young and elderly patients. Overall, the number of deaths was similar between the treatment groups (17 moxifloxacin, 19 comparator).

Conclusions: Drug-related adverse event rates associated with oral moxifloxacin or the comparator therapy used in these studies did not significantly increase with

advancing age. This pooled analysis suggests that oral moxifloxacin can be safely used in elderly patients with characteristics consistent with those enrolled into the clinical trials.

Background

As individuals age, they undergo physiological changes that alter their responses to infection and to ensuing treatment. Not only are elderly persons at greater risk of infection than younger patients, but these infections are associated with a higher rate of morbidity and mortality.[1] It is, therefore, crucial that therapeutic agents be evaluated in the elderly in order to determine their safety, including their impact on renal or hepatic impairment and the risks of drug-drug interactions (DDIs). Moxifloxacin is a 'respiratory' fluoroquinolone that is available both in oral and intravenous (IV) formulations.[2,3] Its once-a-day formulation, broad spectrum of activity[4] and lack of clinically significant DDIs[5] suggest that moxifloxacin may be effective and safe in the elderly population.

Aging is often accompanied by reduced renal function and by declines in creatinine clearance levels (i.e. approximately 40% decline between middle age and >80 years of age).[6] As such, reduced doses are often required in older patients with impaired renal function. Unlike most other fluoroquinolones that primarily have a route of renal excretion, moxifloxacin is primarily (76%) excreted by non-renal routes (20% renal, 51% hepatic and 25% trans-intestinal). As a result, the elimination half-life is not significantly prolonged in patients with reduced creatinine clearance.[5] Because moxifloxacin has dual routes of excretion, no dose adjustments are required in patients with renal impairment or mild to moderate hepatic insufficiency.[7] The pharmacokinetics of moxifloxacin in patients with severe hepatic insufficiency has not been studied. Unpublished data in a small number of healthy elderly volunteers (eight men, eight women) did not reveal any clinically significant age or sex-related differences in the area under the concentration-time curve (AUC) or peak plasma drug concentration (C_{max}).[8]

The minimal DDI profile of moxifloxacin also makes this drug well suited for the elderly, who often require multiple therapies.[5,9] Moxifloxacin is not associated with drug-interactions secondary to altered hepatic metabolism because moxifloxacin is not metabolised via the cytochrome P450 system, which does metabolise other drugs.[5] Of importance, diabetic patients taking glibenclamide (glyburide) concurrently with moxifloxacin, have not developed clinically relevant hypo- or hyperglycaemia.[10] Therefore, no additional monitoring of blood sugars is required when moxifloxacin is administered to patients with diabetes mellitus.

To address the safety of oral moxifloxacin in elderly patients beyond pharmacokinetic and DDI studies that have already been reported, a retrospective analysis of adverse events in the elderly was performed on 27 trials that comprised the Bayer clinical trial database (table I).

Materials and Methods

Study Design

The Bayer clinical trial database, which includes data from all phase II and phase III clinical trials on oral moxifloxacin conducted between June 1996 and December 2001, was used in this analysis. Patients were pooled from a total of 27 randomised, prospective, controlled trials in order to evaluate the safety profile of moxifloxacin in the elderly (table I). In all trials, treatment with oral moxifloxacin 400mg once daily was contrasted to treatment with a comparator antibacterial. The comparator drugs were cefuroxime (n = 1239), clarithromycin (n = 1166), levofloxacin (n = 581), amoxicillin/clavulanic acid (n = 566), trovafloxacin (n = 553), ofloxacin (n = 517), cefalexin (n = 450), doxycycline (n = 326), azithromycin (n = 284), amoxicillin (n = 247), cotrimoxazole (trimethoprim/sulfamethoxazole) [n = 25] and cefixime (n = 7). Dose regimens for comparator agents were disease-state specific and were in accordance with local labelling and the recommendations of the manufacturer.

Table I. List of the 27 phase II/III/IIIb clinical studies comprising the Bayer clinical trials database for moxifloxacin

Study number, (region)[a]	Phase	Design	Moxifloxacin regimen	Duration (days)	Comparator regimen	Duration (days)
Acute sinusitis						
0109 (EU)	II	r, op, pc, pg	200mg od and 400mg od	7–14	Clarithromycin/500mg bid	7–14
0126 (NA)	III	r, db, pc, pg	400mg od	7	Cefuroxime/250mg bid	10
0116 (EU)	III	r, db, pc, pg	400mg od	7	Cefuroxime/250mg bid	10
0161 (EU)	III	r, db, pc, pg	400mg od	10	Cefuroxime/250mg bid	10
100107 (NA)	IIIb	r, db, pc, pg	400mg od	10	Cefuroxime/250mg bid	10
10031 (EU)	IIIb	r, op, pc, pg	400mg od	10	Amoxicillin/clavulanic acid/500mg/125mg	10
100161 (NA)	IIIb	r, db, pc, pg	400mg od	10	Trovafloxacin/200mg od	10
400012 (EU)	IIIb	r, db, pc, pg	400mg od	7	Trovafloxacin/200mg od	10
Acute exacerbations of chronic bronchitis						
0106 (EU)	II	r, db, pc, pg	200mg od and 400mg od	6 –14	Cefixime/400mg od	6–14
0128 (NA)	III	r, db, pc, pg	200mg od and 400mg od	10	Cefuroxime/500mg bid	10
0127 (NA)	III	r, db, pc, pg	400mg od	5 and 10	Clarithromycin/500mg bid	10
84 (EU)	IIIb	r, op, pc, pg	400mg od	5	Amoxicillin/clavulanic acid/500mg/125mg	7
10035 (O)	IIIb	r, db, pc, pg	400mg od	5	Levofloxacin/500mg od	7
100243 (NA)	IIIb	r, db, pc, pg	400mg od	5	Levofloxacin/500mg od	7
0124 (EU)	III	r, db, pc, pg	400mg od	5	Clarithromycin/500mg bid	7
100160 (NA)	IIIb	r, db, pc, pg	400mg od	5	Azithromycin/250mg od	5
Community-acquired pneumonia						
0112 (O)	II	r, db, pc, pg	200mg od and 400mg od	5–14	Amoxicillin/500mg tid	5–14
0119 (EO)	III	r, db, pc, pg	200mg od and 400mg od	10	Clarithromycin/500mg bid	10
0130 (NA)	III	r, db, pc, pg	400mg od	10	Clarithromycin/500mg bid	10
0140 (EO)	III	r, db, pc, pg	400mg od	10	Amoxicillin/1000mg tid	10
Skin and skin structure						
0122 (O)	II	r, db, pc, pg	200mg od and 400mg od	5–14	Cefalexin/500mg tid	5–14
0131(O)	III	r, db, pc, pg	400mg od	5–14	Cefalexin/500mg tid, (+) or (–) MET/400mg tid	5–14
0158 (NA)	III	r, db, pc, pg	400mg od	7	Cefalexin/500mg tid	7
Uncomplicated urinary tract infection						
0114 (NA)	II	r, db, pc, pg	400mg od	7	TMP/SMX/160/800mg bid	7
Complicated urinary tract infection						
0121 (EO)	III	r, db, pc, pg	400mg od	7–14	Ofloxacin/200mg bid	7–14
Uncomplicated pyelonephritis						
0134 (EU)	IIIb	r, db, pc, pg	400mg od	7–10	Ofloxacin/200mg od	7–10
Pelvic inflammatory disease						
0118 (EO)	III	r, db, pc, pg	400mg od	10–14	MET/400mg tid (+) doxycycline/100mg bid (+) 1x ciprofloxacin/500mg	10–14

a Geographical region where study was conducted: NA = North America; EU = Europe; EO = Europe and other countries (excluding North America); O = ex-NA and ex-EU.

bid = twice daily; **db** = double-blind; **MET** = metronidazole; **od** = once daily; **op** = open label; **pc** = placebo-controlled; **pg** = parallel group; **r** = randomised; **tid** = three times daily; **TMX/SMX** = cotrimoxazole (trimethoprim/sulfamethoxazole); **u** = uncontrolled.

Several characteristics of the pooled safety population deserve special mention. In each trial, there was no upper age limit. Enrolment was not restricted based on functional status. Patients with an impaired mental status were excluded only if the patient was not deemed competent to give informed consent and did not have a family member who could provide informed consent for the patient. With the exception of type 1 and type 3 antiarrhythmics, which are known to prolong the corrected QT (QTc) interval, patients enrolled in these trials were permitted to take all other prescribed medications. Accordingly, the pooled analysis represents a real-world elderly population.

Safety Population

Data from a total of 12 231 patients were analysed for safety, including 6270 moxifloxacin- and 5961 comparator-treated patients. A total of 42 countries participated in these studies with the US enrolling the most patients (4985), followed by France (874), Mexico (787), Germany (754), South Africa (706), UK (637) and Greece (407). There were 9671 (79.0%) patients who were <65 years of age, 1636 (13.4%) patients 65–74 years of age and 924 (7.6%) patients ≥75 years of age (range 75–95 years of age in the moxifloxacin group and 75–97 years of age in the comparator group). Within the <65 years of age group, most men (61%) were between the 18 and 44 years of age, 39% were between 45 and 64 years of age and 13 patients were <18 years of age.

Safety and Tolerability Endpoints

The safety population included all patients in the pooled analysis who received at least one dose of study medication. This analysis evaluated five primary endpoints: treatment-emergent adverse events; drug-related adverse events (a subset of the former endpoint); serious drug-related adverse events; deaths; and premature discontinuation of study drug therapy. Each endpoint was part of the original study design for the 27 studies. In general, systemic surveillance of adverse events was captured via careful questioning of the patient, physical examination and routine laboratory testing. The methodological details for the evaluation of glucose levels following moxifloxacin therapy have been summarised in a separate report.[10]

Treatment-emergent adverse events were defined as any adverse event regardless of relationship to treatment. Drug-related adverse events were those treatment-emergent adverse events that an investigating physician estimated to be possibly or probably related to the study medication. Each treatment emergent adverse event was graded by the investigator with respect to severity (mild, moderate or severe) and evaluated in terms of seriousness (events which were fatal, life-threatening, required hospitalisation/prolongation of hospitalisation, resulted in disability or otherwise medically important event). All treatment-emergent events were coded using COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms). Subsequently, all treatment-emergent and drug-related adverse events were stratified by patient age (<65 years of age, 65–74 years of age, ≥75 years of age).

Information regarding the premature discontinuation of moxifloxacin or a comparator agent because of a treatment-emergent adverse event was also collected from the database, as well as information as to whether the event resolved spontaneously or with medical intervention. Deaths, and their causality to study drug, were also recorded.

Serial 12-lead ECG monitoring was performed in several of the studies, but was not required by all. The methods used to detect moxifloxacin-induced QT interval prolongation were consistent with the standard of practice at the time the studies were conducted.

Statistical Analysis

Three different statistical analyses were performed for three of the primary outcomes: (i) premature termination of study drug because of treatment-emergent adverse events; (ii) overall rates of treatment-emergent adverse events; and (iii) overall rates of drug-related adverse events. No statistical testing was performed for serious drug-related adverse events and deaths because of the small number of observations in these groups.

Cochran-Mantel-Haenszel χ^2 tests were used to test the null hypothesis of no difference in the incidence rates of premature terminations between

Table II. Patient demographics of the safety population

Demographic	Moxifloxacin			Comparator		
	<65 years of age (n = 4939)	65–74 years of age (n = 842)	≥75 years of age (n = 489)	<65 years of age (n = 4732)	65–74 years of age (n = 794)	≥75 years of age (n = 435)
Male sex, n (%)	2105 (43)	467 (56)	314 (64)	2039 (43)	436 (56)	278 (64)
Race, n (%)						
Caucasian	3245 (66)	683 (81)	395 (81)	3134 (66)	610 (77)	357 (82)
Black	776 (16)	29 (3)	15 (3)	690 (15)	35 (4)	5 (1)
Asian	108 (2)	12 (1)	4 (1)	116 (3)	7 (1)	4 (1)
Hispanic	104 (2)	6 (1)	3 (1)	82 (2)	10 (1)	2 (1)
Native American	8 (<1)	0	0	5 (<1)	1 (<1)	0
other[a]	572 (12)	112 (13)	67 (14)	577 (12)	131 (16)	67 (15)
Mean age (years [SD])	41 (13)	69 (3)	80 (4)	40 (13)	69 (3)	80 (4)
Mean weight[b] (kg [SD])	75 (20)	75 (16)	71 (15)	74 (18)	74 (16)	69 (14)
Mean number (SD) of underlying medical conditions[c]	4.1 (3.5)	6.0 (4.8)	6.7 (5.0)	4.0 (3.5)	5.6 (4.4)	6.2 (4.7)

a Other included missing, unknown, not reported and other.

b In the <65 years of age, 65–74 years of age and ≥75 years of age groups, weight measurements were missing for 28, 4 and 5 patients in the moxifloxacin group and 32, 7 and 5 patients in the comparator group, respectively.

c Numbers reflect only those patients who reported at least one medical condition (n = 9684).

SD = standard deviation.

patients in the moxifloxacin group and patients in the comparator group.[11] This test was adjusted for the three age groups studied.

χ^2 tests were used to test the null hypothesis of no difference in the incidence rates of treatment-emergent and drug-related adverse events between patients in the three age groups studied. These tests were performed separately within moxifloxacin and comparator group patients.

A treatment by age group interaction test was performed to determine if the comparison between moxifloxacin and the comparator group, with respect to incidence rates of any treatment-emergent adverse event and any drug-related adverse event, was affected by increasing age. A logistic regression analysis was used to test for this interaction; the regression included effects for treatment, age group and treatment by age group interaction.[12]

Results

Analysis of the pooled data revealed that, with the exception of one trial, patients were equally distributed among treatment groups (6270 patients in the moxifloxacin group and 5961 in the comparator group). One trial randomised 309 more moxifloxacin patients than the comparator group because the study was designed to evaluate two different regimens of moxifloxacin. Demographic characteristics between the moxifloxacin and comparator populations are outlined in table II. Interestingly, the percentage of males and of Caucasian patients increased with age from 43% and 66% of patients <65 years of age to 64% and 80% of patients ≥75 years of age, respectively. Similarly, the average number of co-morbidities were generally lower for patients <65 years of age (approximately four underlying medical conditions) than for patients ≥65 years old (approximately six medical conditions) [table II]. The difference in the mean number of co-morbidities was statistically significant between the younger and two older age groups ($p < 0.01$ for both comparisons for moxifloxacin and control). Furthermore, there were no disparities in the proportion of patients with co-morbid conditions between the treatment groups when they were stratified by age. Specifically, for moxifloxacin-treated patients at least one co-morbid condition was reported in 75.8% of those <65 years of age, 93.0% for those 65–74 years of age and 92.4% for those ≥75 years of age. Corresponding data for the control group were 75.2%, 92.4% and 94.9%, respectively.

A significantly greater proportion of elderly patients (>90%) were also receiving one or more con-

Table III. Patient treatment status of enrolled patients[a]

Outcome	Moxifloxacin			Comparator		
	<65 years of age (n = 4984)	65–74 years of age (n = 848)	≥75 years of age (n = 489)	<65 years of age (n = 4770)	65–74 years of age (n = 796)	≥75 years of age (n = 435)
Completed treatment, n (%)	4495 (90)	777 (92)	445 (91)	4328 (91)	734 (92)	396 (91)
Premature termination, n (%)	487 (9)	71 (8)	44 (9)	442 (9)	62 (8)	39 (9)
Treatment-emergent adverse event, n (%)	174 (4)	31 (4)	23 (5)	163 (3)	30 (4)	24 (6)
Insufficient therapeutic effect, n (%)	45 (1)	12 (1)	6 (1)	46 (1)	11 (1)	5 (1)
Death – any cause, n (%)	2 (<1)	6 (<1)	9 (1.8)	11 (<1)	2 (<1)	6 (1.4)

a Discontinuations because of patient non-compliance, consent withdrawn, patient lost to follow-up, protocol violation, cure, organism resistant to drug or investigator request, occurred in ≤1% of any treatment group.

comitant medications than patients who were <65 years of age (~71%; $p < 0.001$).

Most patients (>90%) completed treatment. Premature discontinuation of oral moxifloxacin because of a treatment-emergent adverse event in the elderly population comprising this retrospective study was low (range 4–5%) and comparable to other conventional antibacterial regimens (range 4–6%). Furthermore, premature discontinuations because of treatment-emergent adverse events were equally distributed between treatment groups ($p = 0.359$) and were not affected by age ($p = 0.389$ for moxifloxacin age effect and $p = 0.078$ for comparator group age effect) [table III]. Differences in the rates of premature termination between the moxifloxacin and comparator groups did not increase with age ($p = 0.552$).

The mean duration of treatment was similar for the moxifloxacin and comparator treatment groups in all three age stratifications. For those patients <65 years of age, mean duration of therapy was 9.1 days (122 person years of exposure) for moxifloxacin versus 9.3 days (120 person years of exposure) for the comparator drugs. For patients ranging from 65 to 74 years of age, the mean duration of therapy was 8.2 days (19 person years of exposure) for moxifloxacin versus 8.5 days (18 person years of exposure) for comparators. Finally, for patients ≥75 years of age, the mean duration of therapy was 8.4 days (11 person years of exposure) for moxifloxacin versus 8.4 days (10 person years of exposure) for the comparator drugs.

The primary purpose of this pooled safety analysis was to determine whether increasing age resulted in more adverse events attributable to moxifloxacin. Within the moxifloxacin group, examination of treatment-emergent adverse events revealed no significant differences across the three age groups ($p = 0.599$) [table IV]. There was a significant difference in the incidence rate of moxifloxacin drug-related adverse events across the three age groups ($p = 0.001$) but surprisingly, this difference was primarily related to increased drug-related adverse events in the younger patient population and *not* in the elderly patient groups. Thus, in moxifloxacin-treated patients, the incidence of nausea, vomiting, dyspepsia and vaginal moniliasis was significantly greater in younger men or women (<65 years) versus the elderly, whereas the rate of insomnia appeared to increase with age (table IV). Within the comparator treatment group, rates of treatment-emergent and drug-related adverse events did not differ across the three age groups ($p = 0.845$ and $p = 0.079$, respectively). However, nausea, dizziness and elevated γ-glutamyl transpeptidase levels occurred more frequently in patients who were <65 years of age.

The difference between the moxifloxacin group and the comparator group in the number of patients who reported a treatment-emergent adverse event did not increase with age ($p = 0.83$). Similarly, the difference in the rates of drug-related adverse events between the moxifloxacin group and comparator group were also not affected by increasing age ($p = 0.43$). Accordingly, these analyses indicate that the comparison of the adverse events between moxifloxacin and comparator is not affected by increasing age.

Serious drug-related adverse events were rare and only increased from 0.5% to 1.0% with increasing age regardless of treatment group (table V). No marked differences between moxifloxacin and comparator treatment groups were observed in this

Table IV. Number of patients with treatment-emergent and drug-related adverse events in the safety population

Adverse event	Moxifloxacin			Comparator		
	<65 years of age (n = 4939)	65–74 years of age (n = 842)	65–74 years of age (n = 489)	<65 years of age (n = 4732)	65–74 years of age (n = 794)	65–74 years of age (n = 435)
Any treatment-emergent adverse event (%)	2161 (43.8)	382 (45.4)	221 (45.2)	2056 (43.4)	351 (44.2)	194 (44.6)
Any drug-related adverse event (%)	1344 (27.2)	183 (21.7)	111 (22.7)	1154 (24.4)	169 (21.3)	93 (21.4)
Drug-related adverse events occurring in >1% of patients (%)						
Digestive system						
nausea	381 (7.7)	40 (4.8)	19 (3.9)	260 (5.5)	35 (4.4)	11 (2.5)
diarrhoea	274 (5.5)	39 (4.6)	29 (5.9)	236 (5.0)	28 (3.5)	21 (4.8)
vomiting	89 (1.8)	5 (0.6)	6 (1.2)	80 (1.7)	8 (1.0)	3 (0.7)
dyspepsia	72 (1.5)	8 (1.0)	1 (0.2)	59 (1.2)	8 (1.0)	3 (0.7)
abnormal liver function test	58 (1.2)	11 (1.3)	3 (0.6)	55 (1.2)	6 (0.8)	9 (2.1)
flatulence	37 (0.7)	2 (0.2)	1 (0.2)	25 (0.5)	4 (0.5)	6 (1.4)
GGTP increased	8 (0.2)	0	0	11 (0.2)	1 (0.1)	5 (1.1)
Body as a whole						
headache	91 (1.8)	12 (1.4)	4 (0.8)	101 (2.1)	12 (1.5)	4 (0.9)
abdominal pain	106 (2.1)	10 (1.2)	8 (1.6)	81 (1.7)	13 (1.6)	4 (0.9)
asthenia	48 (1.0)	7 (0.8)	4 (0.8)	43 (0.9)	3 (0.4)	4 (0.9)
Nervous system						
dizziness	123 (2.5)	30 (3.6)	12 (2.5)	116 (2.5)	9 (1.1)	5 (1.1)
insomnia	23 (0.5)	0	5 (1.0)	32 (0.7)	2 (0.3)	3 (0.7)
Skin and appendages						
rash	44 (0.9)	3 (0.4)	6 (1.2)	33 (0.7)	7 (0.9)	1 (0.2)
Special senses						
taste perversion	45 (0.9)	7 (0.8)	5 (1.0)	67 (1.4)	18 (2.3)	9 (2.1)
Urogenital system						
vaginal moniliasis	53 (1.1)	0	0	40 (0.8)	2 (0.3%)	1 (0.2)

GGTP = γ-glutamyl transpeptidase.

Table V. Number of patients with serious drug-related adverse events in the safety population

Adverse events	Moxifloxacin			Comparator		
	<65 years of age (n = 4939)	65–74 years of age (n = 842)	≥75 years of age (n = 489)	<65 years of age (n = 4732)	65–74 years of age (n = 794)	≥75 years of age (n = 435)
Any body system (%)	24 (0.5)	5 (0.6)	5 (1.0)	26 (0.5)	5 (0.6)	4 (0.9)
Body as a whole (%)	11 (0.2)	1 (0.1)	0	9 (0.2)	1 (0.1)	0
Cardiovascular system (%)	3 (<0.1)	1 (0.1)	1 (0.2)	3 (<0.1)	1 (0.1)	1 (0.2)
Digestive system (%)	4 (<0.1)	0	1 (0.2)	5 (0.1)	2 (0.3)	1 (0.2)
Endocrine system (%)	1 (<0.1)	0	0	0	0	0
Haemic/lymphatic system (%)	2 (<0.1)	1 (0.1)	0	1 (<0.1)	0	0
Metabolic/nutritional disorder (%)	0	0	0	2 (<0.1)	1 (0.1)	0
Nervous system (%)	1 (<0.1)	0	0	2 (<0.1)	0	1 (0.2)
Respiratory system (%)	4 (<0.1)	2 (0.2)	3 (0.6)	5 (0.1)	1 (0.1)	0
Skin and appendages (%)	3 (<0.1)	0	0	1 (<0.1)	1 (0.1)	0
Special senses (%)	1 (<0.1)	0	0	0	0	0
Urogenital system (%)	1 (<0.1)	1 (0.1)	0	3 (<0.1)	0	1 (0.2)

database for any serious drug-related adverse event category (overall rates of 0.5% for moxifloxacin versus 0.6% for comparator). Serious drug-related adverse events experienced by at least three patients who received either moxifloxacin or a comparator, irrespective of age, included pelvic pain, diarrhoea, vomiting, leukopenia and respiratory disorders. Three cases of serious abdominal pain were reported in the comparator group in patients who were <65 years of age, but not in the moxifloxacin group. No serious drug-related adverse events related to glucose homeostasis were reported in either treatment group.

Of clinical relevance, drug-related cardiovascular adverse events categorised as serious in the 27 studies were very rare (<1%) and not related to the age of the patient. These adverse events, which occurred in no more than one patient per age and treatment group, included tachycardia, extrasystoles, QT interval prolongation, deep thrombophlebitis, hypotension, migraine, postural hypotension, atrial fibrillation and palpitation. ECG analyses were performed in a total of 787 patients with paired-valid 12-lead ECGs (obtained pre-therapy and on study day 3 of oral moxifloxacin administration) during an extensive investigation of potential moxifloxacin-related cardiovascular effects. Of these patients, 651 were <65 years of age and 136 were ≥65 years of age. Mean QTc interval prolongation for patients <65 years was 7 ± 25 msec compared with 2 ± 28 msec for patients ≥65 years ($p = 0.055$). No arrhythmias related to QTc interval prolongation and no preponderance of significant QTc interval prolongation were observed among the elderly in both the moxifloxacin and comparator groups. No QTc interval prolongation-related deaths occurred in either the moxifloxacin or comparator treatment group.

A total of 36 deaths (17 moxifloxacin group, 19 comparator group) were reported from this pooled database (table III). In the moxifloxacin group, two deaths occurred in patients who were <65 years of age, six in those 65–74 years of age, and nine in those ≥75 years of age. The majority of deaths occurred after moxifloxacin therapy had been completed (15 of 17) and were related to underlying comorbid conditions. Of the two deaths that occurred during moxifloxacin therapy (day 4 and 11), one death of a 74-year-old man was related to complications of severe infection and the other, in a 87-year-old man, was related to underlying chronic bronchitis and cor pulmonale. In the comparator group, 11 deaths occurred in patients who were <65 years of age, 2 in those 65–74 years of age and 6 in those ≥75 years of age. All deaths in the comparator group occurred after completion of antimicrobial therapy. Of the 36 deaths reported, 2 deaths in the moxifloxacin-treated patients and 4 deaths in the comparator-treated patients were considered to be due to progression of the underlying infectious process. None of the deaths in the moxifloxacin or comparator group were considered to be related to study drug therapy.

Discussion

Moxifloxacin has proven clinical efficacy as a monotherapy regimen against common and atypical respiratory pathogens and provides the clinician with the option of sequential therapy (IV and oral formulations). High tissue and inflammatory cell penetration,[13-15] proven pharmacokinetic/pharmacodynamic profile and minimal DDIs represent further features associated with the utility of moxifloxacin in the clinical setting. Although moxifloxacin does not appear to have a high rate of untoward adverse reactions,[16-20] the safety and tolerability of this quinolone has not been well characterised in the elderly population. Accordingly, the current safety analysis, which includes approximately 2500 elderly patients (>64 years of age), provides valuable evidence of the safety profile of moxifloxacin in this older patient population.

The primary purpose of this pooled analysis was to examine if the elderly experienced more adverse events attributable to either moxifloxacin or the comparator regimen than patients <65 years of age. Two separate analyses, a treatment by age group interaction test and a χ^2 test confirmed that the rates of most observed moxifloxacin-related adverse events in this population did not increase with age. Although the χ^2 test showed an age effect for moxifloxacin drug-related events across the three age groups, further analysis found that elderly patients (i.e. those >64 years of age), in fact, had significantly lower rates of drug-related gastrointestinal adverse events (nausea, vomiting and dyspepsia) than the younger cohort ($p < 0.05$), whereas insomnia appeared to increase with age ($p = 0.024$). Although the higher rate of insomnia in the elderly may simply be attributable to older age, it is also possible that concomittant medications, including moxifloxacin,[21] as well as co-morbid conditions, may individually or synergistically be responsible for this adverse effect. Rates of drug-related adverse events were not influenced by age for the comparator regimen.

Serious drug-related adverse events were rare and did not significantly increase with age for either the moxifloxacin or comparator regimen. Importantly, no drug-related deaths occurred, with 17 total deaths reported in the moxifloxacin group versus 19 in the comparator group. In both the moxifloxacin and comparator groups, more deaths occurred in the oldest groups (≥75 years of age), although this was often attributed to underlying co-morbid conditions and not to antimicrobial treatment or the current infection.

This pooled analysis has several strengths and limitations. The database included a large number of patients (>12 000), thereby permitting a thorough analysis of safety and tolerability between the moxifloxacin and comparator regimens. Although we did not find that increasing age led to more moxifloxacin-related adverse events, the numbers of patients comprising the two older age groups (i.e. 65–74 years of age and ≥75 years of age) were smaller than the numbers of patients who were <65 years of age. Thus, it is possible that our findings do not estimate true rates of adverse events in the elderly population. However, the numbers of patients in each group were substantial. Our analysis was also hampered by its retrospective design, although the rates of moxifloxacin-related adverse events do not differ from those reported in the smaller prospective clinical trials. The findings in this pooled analysis were consistent with other prospective fluoroquinolone studies that evaluated safety in the elderly.[22-26] Although geriatric patients may be at greater risk for adverse effects due to underlying diseases and co-morbid conditions, as well as concomitant medications, fluoroquinolones have not been associated with higher rates of adverse events or of premature discontinuations than with younger populations.[22-26] As in younger patients, older patients treated with moxifloxacin in our analysis reported gastrointestinal (nausea, diarrhoea) and CNS (dizziness) adverse effects most often.[27,28] These effects are associated, to varying degrees, with all available fluoroquinolones. Importantly, our analysis failed to reveal any hypo- or hyperglycaemic effects possibly attributable to moxifloxacin.

No arrhythmias related to QTc interval prolongation were reported following oral moxifloxacin treatment in this large group of young and elderly patients. The elderly did not have a higher incidence of significant QTc interval prolongation and advanced age (≥65 years of age) did not serve as a predictor of greater QTc interval prolongation.

However, because only a small proportion of younger and older patients (<12%) had valid paired ECGs performed during these trials, these data need to be viewed cautiously.

Conclusion

In summary, based on the findings of this large retrospective analysis, oral moxifloxacin was well tolerated for the treatment of community-acquired infections in elderly patients. Notably, rates of drug-related adverse events between the moxifloxacin and comparator groups were not affected by increasing age. No new or unexpected adverse reactions attributable to moxifloxacin were found in more than 1300 geriatric patients who were evaluated. Accordingly, clinicians may consider oral moxifloxacin as a safe antibacterial option for the treatment of infections in older patients who have characteristics similar to those enrolled in trials in this pooled analysis. Prospective studies are needed to further evaluate the safety of moxifloxacin in the elderly.

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