Absence of respiratory effects with ivabradine in patients with asthma

K. Suresh Babu, Frantisek Gadzik¹ & Stephen T. Holgate

Infection, Inflammation and Repair, Southampton General Hospital, Southampton, UK and

¹*Department of Clinical and Immuno Pharmacology, Institute of Preventive and Clinical Medicine, Bratislava, Slovakia*

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Ivabradine is a new heart rate-lowering agent that acts specifically on the sinoatrial node via the I_f pacemaker channels.
- Ivabradine has demonstrated similar efficacy to β -blockers.
- As β -blockers are contraindicated in patients with obstructive airway disease, this study was conducted to assess the safety of ivabradine in patients with asthma.

WHAT THIS STUDY ADDS

- This study demonstrates that ivabradine has no effect on the pulmonary functions in patients with asthma and can be safely used as a heart rate-lowering agent in patients with angina and coexistent airflow obstruction.

Correspondence

Dr K. S. Babu,
Mailpoint 810, Level F, South Block,
Southampton General Hospital,
Southampton SO16 6YD, UK.
Tel: + 44 79 6898 7873
Fax: + 44 23 8077 0202
E-mail: sureshbabu97@gmail.com

Keywords

adrenergic β -antagonists, angina pectoris, asthma, bronchoconstriction, ivabradine, respiratory function

Received

19 July 2007

Accepted

1 February 2008

Published OnlineEarly

13 March 2008

AIM

β -Blockers are commonly prescribed for stable angina and are recommended as initial therapy. However, β -blockers are contraindicated in patients with obstructive airway disease because of a risk of bronchoconstriction. Ivabradine is a specific heart rate-lowering agent that acts via I_f pacemaker channels in the sinoatrial node with no β -adrenoreceptor activity. Ivabradine has been recently approved for the treatment of stable angina. This study assessed the effects of repeated administration of ivabradine on lung function in patients with asthma.

METHODS

In this double-blind, placebo-controlled, crossover study, 20 subjects with asthma received either oral ivabradine 10 mg b.i.d. or placebo for 4.5 days. Forced expiratory volume in 1 s (FEV_1) and peak expiratory flow rate (PEFR) were designated as the main outcome variable. Diary cards were used to monitor asthma symptoms on a five-point scale, rescue medication usage, and adverse events.

RESULTS

There were no significant differences in mean variation of FEV_1 (ivabradine $P = 0.664$; placebo $P = 0.652$) or PEFR (ivabradine $P = 0.153$; placebo $P = 0.356$) from baseline following administration of ivabradine. There was also no significant difference in maximum percent variation in FEV_1 or PEF between treatment groups ($P = 0.994$; FEV_1 and $P = 0.704$; PEF). On a similar note, there was no significant difference in asthma symptoms or rescue medication usage reported between the two groups. Adverse events were generally mild-to-moderate in intensity and no cardiovascular or serious adverse events were recorded.

CONCLUSIONS

This study confirms that ivabradine does not affect respiratory function or symptoms in patients with asthma and therefore represents a valuable therapeutic alternative to β -blockers for treating patients with stable angina and asthma.

Introduction

Stable angina pectoris is the most prevalent manifestation of coronary artery disease (CAD) and is the initial presentation in nearly 50% of patients [1]. In Europe the prevalence of angina pectoris is estimated to be between 2% and 4% [1]. The incidence of angina increases with age and therefore represents a growing healthcare burden as the population ages and older people are living longer. Angina is associated with an increased risk of myocardial infarction and mortality, and patients experience marked impairment of quality of life [2].

Current antianginal treatments include β -blockers, calcium-channel blockers and nitrates, and are associated with undesirable adverse events. β -Blockers are often prescribed for stable angina and are recommended as first-line treatment option if there are no contraindications [3]. They are contraindicated in patients with asthma and chronic obstructive pulmonary disease (COPD), because of the risk of precipitation of bronchoconstriction [4]. Most of the pulmonary adverse events with β -blockers occurred when β -blockers were used in patients with reversible airway disease [5]. The severity and incidence of bronchoconstriction might be less marked with cardioselective β -blockers, but the risk still remains [6]. There is therefore a clinical need for more cardiospecific antianginal agents for use in patients with coexistent obstructive airway disease.

Ivabradine is the first of a new class of heart rate-lowering agents that act specifically on the sinoatrial node. Ivabradine specifically inhibits the I_f current of cardiac pacemaker cells without affecting other cardiac ionic currents and has no effect on cardiac contractility, repolarization or atrioventricular conduction [7–9]. Ivabradine was recently approved by the European authorities for the treatment of stable angina in patients with contraindication or intolerance to β -blockers. As ivabradine does not interact with adrenoreceptors, it should not modify respiratory function. Ivabradine should therefore be a valuable treatment option for patients with coexistent angina and asthma. This study was carried out to assess the effects of repeated administration of ivabradine at a dose of 10 mg twice daily on respiratory function in patients with asthma but who were otherwise healthy.

Materials and methods

Study design

This double-blind, placebo-controlled, crossover study assessed the effects of repeated administration of ivabradine 10 mg twice daily on respiratory function in patients with asthma. Participants were recruited from two centres, in the UK and Slovakia. Prior to inclusion, subjects were evaluated for respiratory function and eligible patients were randomized to two sequences of treatment.

Treatment sequence was allocated by balanced double-blind randomization.

Patients

Twenty male and female volunteers with documented asthma in accordance with Global Initiative for Asthma guidelines [10] for ≥ 12 months were recruited. The protocol was approved by local ethics committees in both the UK and Slovakia and the study was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent prior to selection. Subjects had a diagnosis of asthma which was well controlled with inhaled corticosteroid treatment (beclomethasone ≤ 1600 mg day⁻¹ or equivalent). They had to be stable for at least 4 weeks prior to enrolment. Inhaled salbutamol (100 μ g per dose) could be used as a rescue medication if needed. Inclusion criteria were: age 18–70 years, heart rate > 50 bpm, forced expiratory volume in 1 s (FEV₁) $\geq 60\%$ of the predicted value, and FEV₁ reversibility to a short-acting bronchodilator (200 μ g of inhaled salbutamol) of $\geq 12\%$. (FEV₁ reversibility is defined as the proportion of reduced lung function that is recovered on administration of a short-acting bronchodilator measured using a spirometer.) Subjects were excluded from the study if they had poorly controlled asthma (defined as hospitalization or emergency department visit during the 6 weeks prior to enrolment), had smoked in the 12 months prior to enrolment, or were unable to understand instructions on dosing, completing diaries, or use of a peak flow meter or metered dose inhaler.

Treatment

Enrolled subjects underwent a 2-week wash-out period (study days –15 to –1), during which concomitant treatments that could affect the study outcomes or interact with ivabradine were forbidden. On inclusion at day 1, baseline characteristics were evaluated, then the first dose of study treatment was taken. Subjects randomized to the ivabradine–placebo (I/P) group received oral ivabradine 10 mg b.i.d. and those randomized to the placebo–ivabradine (P/I) group took a matched placebo. The first treatment period was from day 1 to day 5. On day 5, participants were given the final dose of study treatment in the morning, and then did not receive study drug during a wash-out period on days 6 and 7. On days 8–11, participants then crossed over to receive either ivabradine 10 mg twice daily (P/I group) or placebo (I/P group). The final dose of study drug was taken on the morning of day 12.

Assessments

Subjects were provided with a Wright's mini peak-flow meter to record their peak expiratory flow rate (PEFR) on their diary cards. FEV₁ was measured with a spirometer on days 1, 5, 8 and 12. FEV₁ and PEF were monitored hourly for 6 h on day 1 following administration of the study drug/placebo. PEF was monitored daily by the subjects and was

recorded on the PEF diary issued to them. Asthma symptoms (five-point rating scale) and rescue salbutamol consumption (puffs per day) were recorded in the patients' diaries. Blood pressure and pulse rate were measured by investigators on days 1, 5, 12 and 13 using a mercury sphygmomanometer and counting, respectively. All adverse events were recorded by subjects in their diaries and were assessed, in terms of diagnosis, severity and cause, by investigators. Serious adverse events were defined as any life-threatening adverse event.

Statistical analyses

The randomized population included all subjects who were randomized to study treatment. The per-protocol population was defined as all randomized subjects having completed the study without major protocol deviation. All randomized subjects who received at least one dose of study treatment were included in the safety population.

Mean PEFR and mean FEV₁ were designated as the main activity criteria. Differences in PEFR and FEV₁ between treatments and between sequences of treatment were analysed using two-way analysis of variance (ANOVA). Nonparametric tests were used to see changes in blood pressure and salbutamol use and a *P*-value of <0.05 was considered to be significant. As asthma symptom scores were measured on a five-point rating scale; frequency tables were used for comparison.

Results

Seven male and 13 female subjects were randomized, and 10 were assigned to each sequence of treatment (I/P or P/I). No statistically significant or period effects were seen for FEV₁ or PEFR between study arms (P/I vs. I/P), hence the data from the two groups were pooled.

PEFR

Mean baseline PEFR values ($\pm$ SD) were calculated to be 469.4 ± 155.3 l min⁻¹ for ivabradine and 476.6 ± 122.6 l min⁻¹ for placebo. Mean variation in PEFR over the 6 h following administration of the first treatment (day 1) relative to baseline is shown in Figure 1. Over the 6 h following treatment administration on day 1, no significant differences were found in maximum percentage variation of PEFR between treatments (*P* = 0.704) and no treatment effect was found for either ivabradine or placebo vs. baseline; (*P* = NS). Mean PEFR over 4.5 days (days 1–5 and 8–12 combined) of treatment with ivabradine or placebo was similar before ivabradine treatment (day 1; 469.4 ± 155.3 l min⁻¹) and after repeated administration (day 5; 471.2 ± 167.7 l min⁻¹) (Figure 2). Mean PEFR was also similar 3 h after a single ivabradine dose (day 1; 487.5 ± 166.1 l min⁻¹) and after repeated ivabradine use (day 5; 484.7 ± 141.1 l min⁻¹).

Figure 1

Mean ($\pm$ SD) variation in peak expiratory flow rate (relative to before treatment) on the first day of treatment with ivabradine 10 mg twice daily or placebo (per-protocol population, pooled by treatment, *n* = 19). Ivabradine, (—); Placebo, (---)

FEV₁

Mean FEV₁ ($\pm$ SD) values were 3.18 ± 1.11 l for ivabradine and 3.22 ± 0.98 l for placebo. Mean variation in FEV₁ over the 6 h following administration of study drug relative to baseline is shown in Figure 3. Over the 6 h following treatment administration on day 1, no significant differences were found in maximum percentage variation of FEV₁ between treatments (*P* = 0.990), and no treatment effect was found for either treatment vs. baseline (ivabradine *P* = 0.664; placebo *P* = 0.652).

Mean FEV₁ before (days 1 and 8 combined) and after 4.5 days of ivabradine treatment or placebo (days 5 and 12 combined) is shown in Figure 4. Mean FEV₁ was similar before ivabradine treatment (day 1, 3.18 ± 1.11 l) and after repeated administration (day 5, 3.16 ± 1.02 l). Mean FEV₁ was also similar 3 h after a single ivabradine dose (day 1, 3.20 ± 1.06 l) and after repeated ivabradine use (day 5, 3.11 ± 1.06 l).

Safety

There was no significant difference in the asthma control as evaluated by the symptom scores during the daytime, morning, or night. The use of rescue salbutamol was similar between treatment groups. On day 1, rescue salbutamol usage was 0.9 ± 1.9 puffs for the ivabradine group and 1.0 ± 1.7 puffs for the placebo group. At the end of the study, rescue medication use was similar to that on day 1 (mean $\pm$ SD ivabradine 1.1 ± 2.3 puffs vs. placebo 1.5 ± 2.0 puffs).

Resting heart rate was decreased in the ivabradine group from 67 ± 10 to 54 ± 6 bpm at the end of the treatment period compared with 68 ± 12 to 62 ± 7 bpm in the

Figure 2

Mean ($\pm$ SD) peak expiratory flow rate during 4.5 days of treatment with ivabradine 10 mg twice daily or placebo (pooled by treatment, per-protocol population, $n = 19$). Ivabradine, (—); Placebo, (---)

Figure 3

Mean ($\pm$ SD) variation in forced expiratory volume in 1 s on the first day of treatment with ivabradine 10 mg twice daily or placebo (per-protocol population, $n = 19$). Ivabradine, (—); Placebo, (---)

placebo group. A reduction in heart rate was expected during treatment with ivabradine, due to the drug's mechanism of action, and this did not impact on asthma symptoms or rescue medication use. No significant changes in blood pressure were noted, and all laboratory investigations remained within acceptable ranges throughout the study.

In the safety population ($n = 20$), seven subjects reported a total of 14 adverse events during the study.

Figure 4

Mean ($\pm$ SD) variation in forced expiratory volume in 1 s during the first and last day of treatment with ivabradine 10 mg twice daily or placebo (pooled by treatment, per-protocol population, $n = 19$). Ivabradine, (—); Placebo, (---)

Although 12 adverse events occurred after the first intake of study drug, or occurred prior to inclusion but worsened following administration of study drug, most were considered unrelated to the study drug. No cardiovascular adverse events were reported, and the adverse events recorded during the study (shown in Table 1) were

Table 1

Number of participants experiencing a treatment-emergent adverse event by treatment (safety population, $n = 20$)

Adverse event	Ivabradine (n)	Placebo (n)
Nausea	1	0
Vomiting	0	1
Headache	1	1
Visual symptoms	2	0
Abdominal pain	1	0
Chest pain	0	1
Leg pain	1	0
Fatigue	1	0

generally mild-to-moderate in nature. No serious adverse events occurred during the study. Transient visual symptoms that resolved after discontinuation and were probably related to ivabradine treatment occurred in two subjects.

Discussion

In this study, repeated oral dosing of ivabradine 10 mg twice daily had no significant effect on respiratory function, measured as PEF_R and FEV₁, in otherwise healthy asthmatic patients. Furthermore, there was no difference in asthma symptoms or rescue medication use between the two groups. No serious adverse events were recorded during the study and most adverse events were mild-to-moderate in nature.

Non-selective β -blockers are contraindicated in patients with bronchospastic disorders, such as asthma or COPD [11]. Treatment guidelines state that selective β -blockers may be used in low doses with caution in asthma patients. Nevertheless, as the airways contain both β_1 - and β_2 -adrenergic receptors that cause bronchodilation when activated, even selective β_1 -blockers may cause bronchoconstriction in some patients [12]. Greefhorst and coworkers have demonstrated that β_1 -selective and non-selective β -blockers increased bronchospasm to the same extent [13]. A number of case reports have demonstrated the ability of β -blockers to cause bronchospasm, even in mild asthma [5]. Bronchospasm can be severe, prolonged, and difficult to treat [14], and β -blocker-related bronchospasm is thought to have caused death in a number of patients with asthma [15, 16]. An alternative treatment that does not act through β -adrenergic receptors would therefore be welcome for angina in patients with respiratory disease.

A recent study in the UK has estimated that between 1990 and 1998, the prevalence of physician-diagnosed asthma rose significantly from 3.01% [95% confidence interval (CI) 2.99, 3.03] to 5.14% (95% CI 5.10, 5.18) in

women and from 3.44% (95% CI 3.41, 3.46) to 5.06% (95% CI 5.02, 5.18) in men (P for trend <0.01 for both) [17]. An increase in the prevalence of asthma in the elderly, a population particularly at risk for cardiovascular disease, was also observed. The European Respiratory Society has reported the prevalence of COPD in Europe to be 4–6% [18]. As stated, angina affects approximately 5% of men and 4% of women in the UK. Given that the prevalence of respiratory disease, such as asthma and COPD, is high and increasing, there is now a large and growing potential population of patients with both angina and respiratory disease. Furthermore, there is increasing evidence that there is an increased risk of cardiovascular disease among individuals with asthma, due to hypoxaemia and bronchodilator-induced tachycardia [19].

Ivabradine is the first pure heart rate-lowering agent that has completed clinical development for use in angina. Ivabradine reduces heart rate through selective inhibition of the I_f hyperpolarization-activated Na^+/K^+ channel in the sinoatrial node [7]. The I_f channel is almost unique to nodal cells, so inhibition is highly selective. Ivabradine is therefore free from risk of bronchoconstriction in patients with asthma or COPD. The absence of alteration of respiratory functional parameters and the safety profile recorded in this study strongly support the lack of unwanted cardiovascular or respiratory effects with ivabradine.

The dose of 10 mg b.i.d. used in this study is above the usual recommended doses (5 and 7.5 mg b.i.d.) for the treatment of stable angina, and this provides a substantial safety margin regarding the use of ivabradine in asthmatic patients.

The effect of ivabradine on heart rate was similar to that found in previous studies, which showed that ivabradine lowers heart rate without affecting other electrophysiological processes in both healthy volunteers [8, 20] and angina patients [21].

In conclusion, the results of this study confirm that ivabradine does not affect respiratory function or symptoms in patients with asthma. Ivabradine therefore represents a valuable therapeutic alternative for treating patients with stable angina and comorbid respiratory disease.

Competing interests

S.T.H. is a consultant for Novartis, Synairgen, Merck, Wyeth and Centocor, and has received lecture fees from these companies.

This study was funded by Servier Laboratories, France.

REFERENCES

- 1 Daly CA, Clemens F, Sendon JL, Tavazzi L, Boersma E, Danchin N, Delahaye F, Gitt A, Julian D, Mulcahy D,

- Ruzyllo W, Thygesen K, Verheugt F, Fox KM on behalf of the Euro Heart Survey Investigators. The clinical characteristics and investigations planned in patients with stable angina presenting to cardiologists in Europe: from the Euro Heart Survey of Stable Angina. *Eur Heart J* 2005; 26: 996–1010.
- 2** Staniforth AD. Contemporary management of chronic stable angina. *Drugs Aging* 2001; 18: 109–21.
- 3** Fihn SD, Williams SV, Daley J, Gibbons RJ. Guidelines for the management of patients with chronic stable angina: treatment. *Ann Intern Med* 2001; 135 (8 Pt 1): 616–32.
- 4** Devereux G, Fishwick K, Aiken TC, Bourke SJ, Hendrick DJ. Adverse effects of a single dose of (+)-sotalol in patients with mild stable asthma. *Br J Clin Pharmacol* 1998; 46: 79–82.
- 5** Dart RA, Gollub S, Lazar J, Nair C, Schroeder D, Woolf SH. Treatment of systemic hypertension in patients with pulmonary disease: COPD asthma. *Chest* 2003; 123: 222–43.
- 6** Raine JM, Palazzo MG, Kerr JH, Sleight P. Near-fatal bronchospasm after oral nadolol in a young asthmatic and response to ventilation with halothane. *Br Med J (Clin Res Ed)* 1981; 282: 548–9.
- 7** Bois P, Bescond J, Renaudon B, Lenfant J. Mode of action of bradycardic agent, S 16257, on ionic currents of rabbit sinoatrial node cells. *Br J Pharmacol* 1996; 118: 1051–7.
- 8** Camm AJ, Lau CP. Electrophysiological effects of a single intravenous administration of ivabradine (S 16257) in adult patients with normal baseline electrophysiology. *Drugs R D* 2003; 4: 83–9.
- 9** DiFrancesco D, Camm JA. Heart rate lowering by specific and selective I(f) current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs* 2004; 64: 1757–65.
- 10** National Institute of Health. Global Strategy for Asthma Management and Prevention: 2002. Report no. 02-3659.
- 11** Asirvatham S, Sebastian C, Thadani U. Choosing the most appropriate treatment for stable angina. Safety considerations. *Drug Saf* 1998; 19: 23–44.
- 12** Tafreshi MJ, Weinacker AB. Beta-adrenergic-blocking agents in bronchospastic diseases: a therapeutic dilemma. *Pharmacotherapy* 1999; 19: 974–8.
- 13** Greefhorst AP, van Herwaarden CL. Comparative study of the ventilatory effects of three beta 1-selective blocking agents in asthmatic patients. *Eur J Clin Pharmacol* 1981; 20: 417–21.
- 14** Fujimura M, Abo M, Kamio Y, Myou S, Ishiura Y, Hashimoto T, Matsuda T. Effect of leukotriene and thromboxane antagonist on propranolol-induced bronchoconstriction. *Am J Respir Crit Care Med* 1999; 160: 2100–3.
- 15** Fallowfield JM, Marlow HF. Propranolol is contraindicated in asthma. *BMJ* 1996; 313: 1486.
- 16** Spitz DJ. An unusual death in an asthmatic patient. *Am J Forensic Med Pathol* 2003; 24: 271–2.
- 17** Soriano JB, Kiri VA, Maier WC, Strachan D. Increasing prevalence of asthma in UK primary care during the 1990s. *Int J Tuberc Lung Dis* 2003; 7: 415–21.
- 18** European Respiratory Society. European Lung White Book. Lausanne, Switzerland: European Respiratory Society, 2003; 35–42.
- 19** Suissa S, Assimes T, Brassard P, Ernst P. Inhaled corticosteroid use in asthma and the prevention of myocardial infarction. *Am J Med* 2003; 115: 377–81.
- 20** Manz M, Reuter M, Lauck G, Omran H, Jung W. A single intravenous dose of ivabradine, a novel I(f) inhibitor, lowers heart rate but does not depress left ventricular function in patients with left ventricular dysfunction. *Cardiology* 2003; 100: 149–55.
- 21** Borer JS, Fox K, Jaillon P, Lerebours G. Antianginal and antiischemic effects of ivabradine, an I(f) inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation* 2003; 107: 817–23.