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Cardiovascular safety profile of almotriptan, a new indolic derivative for the treatment of migraine ☆

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Abstract

Almotriptan is a new 5-$HT_{1B/1D}$ receptor agonist effective for treating acute migraine attacks with or without aura. As 3–5% of patients treated with sumatriptan experience chest symptoms thought to be of cardiac origin, we investigated the cardiovascular safety profile of almotriptan in comparison with that of sumatriptan in six animal models. Almotriptan did not modify blood pressure or heart rate in conscious telemetered normotensive Wistar rats (p.o.), in anaesthetised beagle dogs (i.v.), or in conscious beagle dogs (i.v.), and only produced transient increases when administered (s.c.) to telemetered cynomolgus monkeys. Almotriptan did not consistently affect the duration of the electrocardiogram (ECG) intervals in anaesthetised beagle dogs even when the drug was administered into the coronary artery, nor was ECG morphology altered in telemetered cynomolgus monkeys. In contrast, sumatriptan i.v. consistently increased mean blood pressure and heart rate in conscious beagle dogs. Finally, almotriptan did not modify coronary blood flow at a dose of up to 0.3 mg/kg i.v. in conscious beagle dogs. Thus, almotriptan has a favourable cardiovascular safety profile.

Keywords: Cardiovascular safety; 5-$HT_{1B/1D}$ receptor agonist; Migraine; Almotriptan

1. Introduction

Sumatriptan, the first 5-$HT_{1B/1D}$ receptor agonist to reach the market, is effective and generally well-tolerated in acute migraine treatment. According to clinical data, several adverse effects of sumatriptan occur soon after administration, but are transitory and mild (Ottervanger and Stricker, 1995). Chest symptoms affect 3–5% of sumatriptan-treated patients, and are responsible for 10% of decisions to discontinue therapy (Schoenen, 1997). The most frequent chest symptoms are heavy arms (76%) and chest tightness (25%), chest pain being reported only rarely (in around 8%) (Visser and Ferrari, 1997). The mechanism by which chest symptoms are produced is not fully understood, although data suggest that sumatriptan is able to cause coronary vasoconstriction (MacIntyre et al., 1992). Other possible explanations include: sumatriptan-induced pulmonary vasoconstriction (Hillis and MacIntyre, 1993), esophageal spasm (Houghton et al., 1994), intercostal muscle spasm (Epstein et al., 1979) and bronchoconstriction (Inman and Kubota, 1992).

Almotriptan is a new triptan derivative with a high, specific affinity for 5-$HT_{1B/1D}$ receptors (Bou et al., 2000) and a selective profile in experimental models in vivo (Gras et al., 2000). In Phase II clinical studies, almotriptan has proven effective against acute migraine attacks with or without aura (Cabarrocas, 1997). The aim of the present study was to establish the cardiovascular safety profile of almotriptan in comparison with that of sumatriptan in six animal models.

2. Material and methods

2.1. Animals

Male Wistar (CFHB) rats (280–320 g) were supplied by Interfauna Ibérica, (St. Feliu de Codines, Barcelona, Spain). Male Dunkin–Hartley guinea pigs (400–500 g) were supplied by ISOQUIMEN, S.L. (St. Feliu de Codines) and Biocentre (Barcelona, Spain). Beagle dogs of either sex

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(8–16 kg) were supplied by Hazelton (Kalamazoo, MI, USA) or by Almirall (Sant Andreu de la Barca, Spain). Two male cynomolgus monkeys (*Macaca fascicularis*), weighing between 3 and 4 kg, were supplied by CIDA S.A.L. from Shamrock (Small Dole, UK). All animals were fasted for 18 h with water ad libitum before the experiments. All experimental procedures described in this paper were previously notified to the regulatory authorities, and guidelines approved by the Catalan Parliament were strictly followed.

2.2. Methods

2.2.1. Isolated working heart of guinea pig

Guinea pigs were killed by cervical dislocation, and their hearts were removed rapidly and immersed in Krebs–Henseleit solution (118 mM NaCl, 4.7 mM KCl, 25 mM $NaHCO_3$, 1.2 mM $MgCl_2$, 1.0 mM NaH_2PO_4, 2.6 mM $CaCl_2$ and 11.1 mM glucose) at 4°C. The coronary bed was immediately perfused at constant pressure (Langendorff, 1895) with Krebs–Henseleit solution at 37°C bubbled with 95% O_2 plus 5% CO_2. Perfusion of the left auricle (at constant pressure) was initiated after cannulation of the sinus vein. After a 15-min stabilisation period, increasing concentrations (10^{-7} to 10^{-5} M) of either almotriptan ($n = 5$) or sumatriptan ($n = 5$) were infused at 15-min intervals. The data recording system consisted of a pressure transducer type TRI 010 Letica (l'Hospitalet del Llobregat, Spain) connected to Hugo Sachs amplifiers, and an extracorporeal electromagnetic flow probe, type EC4.0-88186 (Skalar, Delft, The Netherlands) connected to a Skalar MDL 1401 flowmeter (Skalar). All signals were recorded on a Watanabe Mark VIII polygraph (Hugo Sachs Elektronik, March-Hugstetten, Germany).

Changes in the maximum drug effects on left ventricular pressure, heart rate, dP/dt max, cardiac output and coronary flow were recorded as percentages of the corresponding baseline values.

2.2.2. Blood pressure in conscious normotensive telemetered rats

Rats ($n = 9$) were implanted with a telemetered pressure transducer fitted with a transmitter (model TA11PA-C40 from Data Science, St. Paul, MN, USA) for recording blood pressure and heart rate via cannulation of the abdominal aorta. The data were processed on an IBM 433DX PS Value Point computer equipped with Dataquest IV, version 2.2 software (Data Science). Almotriptan and sumatriptan were administered at 60 mg/kg by gastric gavage. Mean blood pressure and heart rate were recorded before drug administration and at hourly intervals for up to 24 h afterwards.

This study was planned according to a Latin square design in such a way that, at the end of the assay, each animal had received almotriptan, sumatriptan and vehicle in a randomised order.

2.2.3. Cardiac and haemodynamic effects in anaesthetised beagle dogs

Dogs were anaesthetised with sodium pentobarbital (35 mg/kg i.v. plus a continuous perfusion of 6 mg/kg/h i.v.) and connected to a respirator (Harvard Apparatus, model 607A, Edenbridge, UK) which maintained a constant volume of 10 ml/kg of air, and 15 breaths per min. The animals were kept at a temperature of 37°C throughout the experiment by means of a homeothermic unit (Harvard Apparatus).

A catheter was fitted into the left carotid artery to measure blood pressure and heart rate, and an electromagnetic flow probe placed around the aortic trunk was connected to a Narcomatic RT-500 flowmeter (Narco Bio-Systems, Houston, TX, USA) to measure cardiac output. Intraventricular pressure was recorded via puncture of the left ventricle with a hypodermic needle (22 gauge) connected to a pressure transducer (HP transducer, type #1146-DPT-100, Palo Alto, CA, USA). Left ventricular dP/dt was then calculated as an index of myocardial contractility.

Almotriptan ($n = 3$) or sumatriptan ($n = 3$) was administered in the left femoral vein, at increasing cumulative doses from 1 μg/kg to 3 mg/kg i.v., at 15-min intervals with a perfusion time of 3 min. The effects of the vehicle were not studied. The following parameters were evaluated: mean, systolic and diastolic blood pressures, heart rate, left intraventricular pressure, maximum and minimum values of left ventricular dP/dt, cardiac output, total peripheral resistance, and stroke volume.

2.2.4. Coronary blood flow in conscious normotensive beagle dogs

Dogs ($n = 3$) were fitted with a carotid loop in the left carotid artery (Brown and Korol, 1968) to permit direct measurements of blood pressure. After a post-operative period of at least 15 days, an ultrasound flow probe was implanted in the left descending coronary artery. Animals were anaesthetised with sodium thiopental (20 mg/kg, i.v.) plus inhaled halothane (0.5–1% in room air).

Once the animals had recovered (1 to 2 weeks), they were placed in restraints. Blood pressure was measured using a puncture through the loop in the carotid artery. The flow probe was connected to a Transonic flowmeter (model T101, Transonic Systems, Ithaca, NY, USA). Haemodynamic parameters were recorded on an eight-channel polygraph (model MultiTrace 8, Lectromed, Jersey, UK). The electrocardiogram was recorded on an electrocardiograph (model HP-4760-A, Hewlett-Packard, McMinnville, OR, USA). The main intervals of the electrocardiogram (ECG) (i.e. PR, QRS, QT and QTc according to Bazett, 1920) were measured manually.

This study was planned according to a Latin square design so that, at the end of the assay, each animal had received almotriptan, sumatriptan and vehicle in a randomised order.

Almotriptan and sumatriptan were administered at 15-min intervals at cumulative doses between 0.003 and 0.3 mg/kg, by intravenous perfusion (cephalic vein) over 3 min. The percentage change from baseline was calculated for each parameter.

2.2.5. Blood pressure, heart rate and ECG measurements in conscious cynomolgus monkeys

Two monkeys were implanted with telemetered pressure and ECG transducers fitted with transmitters (model TL10M2-D70-PC by Data Science) for blood pressure and ECG measurements. These signals were processed on a Vectra QS/16S Hewlett Packard computer with software Dataquest IV, version 2.0 (1992, Data Science). The monkeys were anesthetised with ketamine (10 mg/kg, i.m.), atropine (0.05 mg/kg s.c.) and sodium pentobarbital (12.5 mg/kg i.v.).

The following cardiovascular parameters were recorded in unrestrained, freely moving animals: systolic and diastolic blood pressure, heart rate and the QA interval (defined as the interval in milliseconds between the R wave of the ECG and the beginning of the ascending line of the blood pressure curve), and the ECG signal. Compounds were administered subcutaneously from the outside of the thigh. The effect of subcutaneous administration of vehicle was also studied. An interval of ≥ 72 h elapsed between one experimental session and the next.

2.2.6. Intracoronary administration to anaesthetised beagle dogs

Beagle dogs were anaesthetised and prepared as described in Section 2.2.3 above. A left thoracotomy was performed through the fourth intercostal space and the heart was suspended in a pericardial cradle. The left circumflex coronary artery was gently dissected 2 to 4 cm distal to its origin and a polyethylene cannula tipped with a hook-shaped 6 mm long hypodermic needle (25 gauge) was inserted into the lumen of the artery. To avoid blood clotting, a saline solution (0.9% NaCl) was infused at a constant flow of 0.2 ml/min throughout the experiment using an infusion pump. Another polyethylene catheter was inserted into the right common carotid artery for blood pressure and heart rate measurements.

Four-lead surface ECG readings were recorded using an electrocardiograph (Cardiograph HP-4760A, McMinnville, OR, USA). Once the animals were stabilised, the constant infusion of saline was replaced by another containing either vehicle, almotriptan or sumatriptan. The study compounds were administered over a 60-min period at 10 and 30 μg/min doses to separate groups, each consisting of three dogs. Each intracoronary injection was separated by a period of 60 min. The QTc interval was measured according to Bazett's formula (Bazett, 1920).

2.3. Compounds

Almotriptan malate acid or chlorhydrate was synthesised by Ranke (Sant Andreu de la Barca, Spain) and sumatriptan, as a base, was extracted from tablets of Imigran® (Glaxo) in the Medicinal Chemistry Department of Almirall Prodesfarma. In addition the following drugs were used: Sodium pentobarbital (Grindsted Products, Brabant, Denmark), halothane (Fluothane®, Zéneca Farma, Porriño, Spain), ketamine (Imalgène 500®, Rhône Mérieux, El Prat de Llobregat, Spain) and sodium thiopental (Pentothal®, Abbott, Madrid, Spain).

For oral administration, the compounds were dissolved in 0.5% methylcellulose and 0.1% Tween 80, volume

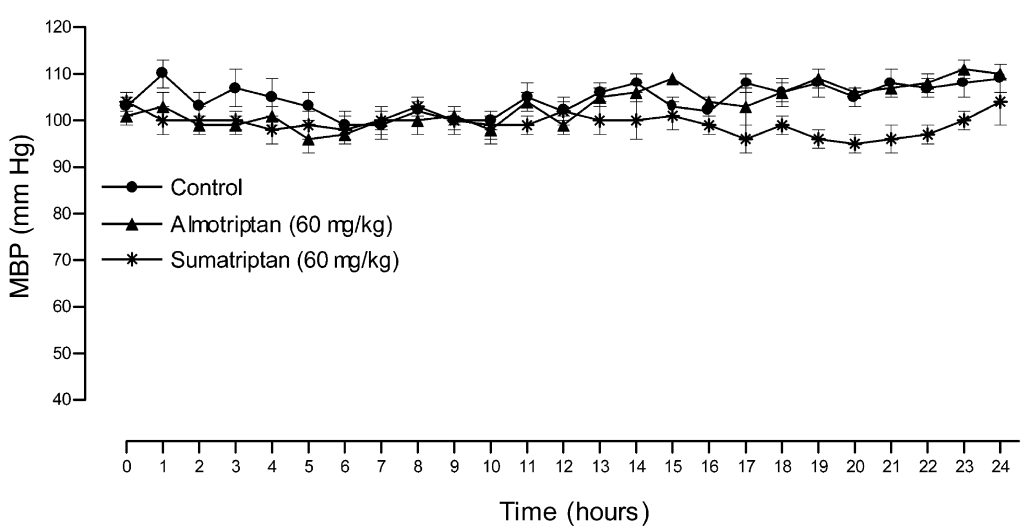

Fig. 1. Effects of almotriptan and sumatriptan (60 mg/kg p.o.) on mean blood pressure (MBP) in telemetered normotensive rats (mean ± S.E.M., $n = 9$). There were no significant differences between the treatments (repeated measures analysis of variance model).

adjusted to 10 ml/kg. When administered intravenously, the compounds were dissolved in 0.9% saline, and slightly acidified with 0.1 N HCl drops to form the salt. In the in vitro study, almotriptan and sumatriptan were dissolved in 10 ml of distilled water and 50 μl of 1 N HCl. All compounds were dissolved to a concentration of 10^{-2} M. Subsequent dilutions were carried out in Krebs–Henseleit solution.

2.4. Statistics

Fisher's protected test procedure was used to test for an overall treatment effect in each repeated measures analysis of variance (ANOVA) model. When the P value for overall treatment effects was greater than (or equal to) 0.05, no other comparisons were done. When the P value was less than 0.05, pairwise treatment comparisons were performed using Student's t-test (SAS, release 6.12, SAS Institute, Cary, NC, USA). See Figs. 1–4 for more details.

3. Results

3.1. Isolated working heart of guinea pig

Sumatriptan and almotriptan, up to 10 μM, had no marked effects (≤ 10% change from baseline). The 10 μM concentration was 25 times higher than that previously observed to contract isolated dog saphenous vein (ED_{50} = 0.39 μM) (Bou et al., 2000).

3.2. Blood pressure in conscious normotensive telemetered rats

Neither almotriptan nor sumatriptan affected mean blood pressure or heart rate in conscious normotensive telemetered rats (Fig. 1).

3.3. Cardiac and haemodynamic effects in anaesthetised beagle dogs

Both almotriptan and sumatriptan showed a slight trend to decrease blood pressure, but clear differences between almotriptan and sumatriptan appeared on analysis of the effects on heart rate and dP/dt_{max}. Sumatriptan produced falls in heart rate and dP/dt_{max} that were significantly different from those seen with almotriptan (ANOVA). The difference for heart rate reached significance from the dose of 0.1 mg/kg onwards, while for the effects on dP/dt_{max} significance of the difference was only reached at 3 mg/kg (Fig. 2).

The other parameters studied showed no major differences between the two compounds, both diminished cardiac output and increased total peripheral resistance, especially at the highest dose tested (i.e. 3 mg/kg). These effects lasted for at least 1 h after administration of the two drugs.

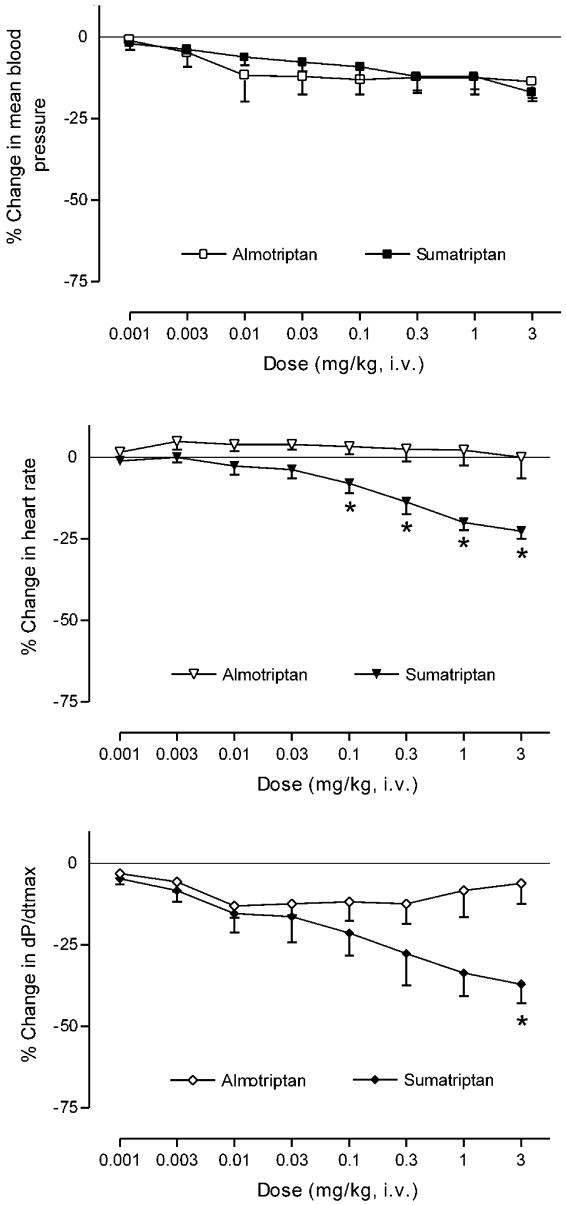

Fig. 2. Effects of i.v. almotriptan and sumatriptan on mean blood pressure (top), heart rate (middle) and dP/dt_{max} (bottom) in open-chest anaesthetised beagle dogs (mean ± S.E.M., $n = 3$). There are overall differences in heart rate and dP/dt_{max} responses between sumatriptan and almotriptan (repeated measures analysis of variance model). Asterisks indicate significant differences between the corresponding doses of the compounds (Student's t test, $^{*}P \leq 0.05$).

3.4. Coronary blood flow in conscious normotensive beagle dogs

Doses of up to 300 μg/kg of almotriptan had no effect on the cardiovascular parameters evaluated. Sumatriptan had no effects at doses up to 10 μg/kg. Above this dose,

a tendency for blood pressure, heart rate and coronary flow to increase was observed (Fig. 3). The overall effects of sumatriptan on heart rate reached statistical significance when compared with those of the vehicle and of almotriptan (ANOVA). However, no significant differences between treatments were observed when pairwise comparisons were made at each dose level. All parameters had returned to baseline values after 24 h.

Almotriptan produced no changes in the ECG intervals evaluated. No changes in ECG morphology were observed either during, or 24 h after, drug administration. No significant changes were observed when the vehicle was administered (Fig. 3).

The animals showed the following symptoms: mydriasis (observed in all dogs with both compounds), lack of coordination in the hind limbs (in two of the three dogs given almotriptan, and in one of the three dogs given sumatriptan) and wet dog shakes.

3.5. Blood pressure, heart rate and ECG in conscious cynomolgus monkeys

Subcutaneous administration of 1 mg/kg of almotriptan had no effect on the parameters evaluated. The dose of 3 mg/kg slightly increased mean blood pressure (from 93 ± 5 to 106 ± 6 mm Hg) and heart rate (from 150 ± 3 to 171 ± 26 beats/min), and decreased the QA interval (from 79 ± 2 to 66 ± 5 ms). All effects were observed during the first h after administration. On the other hand, sumatriptan administered at a dose of 1 mg/kg, increased blood pressure (more evident for systolic blood pressure) and heart rate, and decreased the QA interval slightly. Sumatriptan, 3 mg/kg, increased mean blood pressure (from 98 ± 4 to 112 ± 13 mm Hg) and decreased the QA interval (from 74 ± 4 to 61 ± 4 ms). The effect on heart rate at this dose (from 151 ± 14 to 171 ± 16 beats/min) was less than that detected at 1 mg/kg (from 141 ± 7 to 182 ± 20 beats/min). Such effects were detected only during the first h after drug administration. Small non-significant changes were observed after the administration of vehicle.

A total of 108 electrocardiograms per animal and per treatment were obtained. The QT interval showed little variation after administration of either drug. A slight increase in QT interval was observed during the period of darkness, attributable to the previously mentioned fall in heart rate. This was observed in both monkeys for both almotriptan and sumatriptan, although it was more evident with the latter compound. No morphological ECG alter-

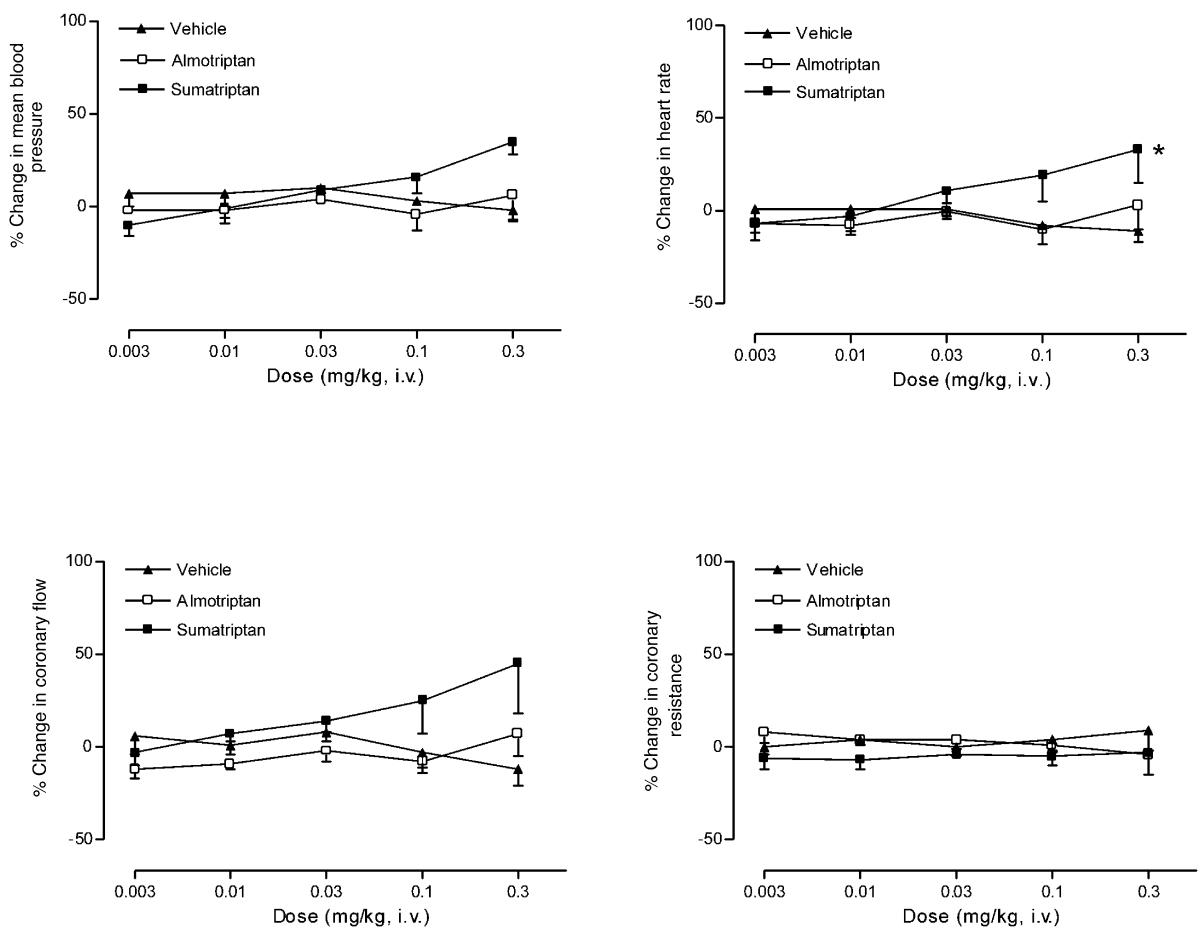

Fig. 3. Effects of i.v. almotriptan, sumatriptan and vehicle on blood pressure, heart rate, coronary flow and coronary resistance in conscious beagle dogs (mean ± S.E.M., $n = 3$). * $P \leq 0.05$ vs. almotriptan and vehicle, overall comparison according to a repeated measures analysis of variance model.

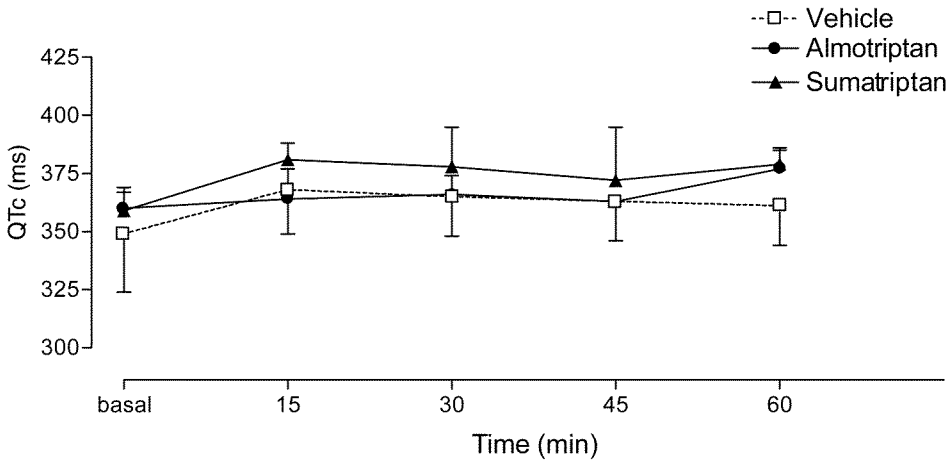

Fig. 4. Lack of effect of almotriptan and sumatriptan on the QTc interval when administered intracoronary (30 μg/min, 1 h) in anaesthetised beagle dogs (mean ± S.E.M., $n = 3$). There were no significant differences between groups (repeated measures analysis of variance model).

ations were observed after administration of either almotriptan or sumatriptan at doses of 3 mg/kg s.c.

The dose of 3 mg/kg of sumatriptan also caused emesis in both animals tested, with onset about 5 min after administration of the compound. The same dose of almotriptan caused emesis in only one of the two monkeys, with later onset. In addition to these emetic effects, vigorous head shaking was observed. This appeared only with the high dose, with no prevalence for a either compound. No mydriasis, salivation or locomotion problems in the hind limbs were observed.

3.6. Intracoronary administration to anaesthetised beagle dogs

Only minor changes were detected in animals treated with vehicle and they could be attributed to the long duration of the experiment. Neither almotriptan nor sumatriptan produced significant changes in mean blood pressure. The effects of both compounds on heart rate were similar to those of vehicle.

Both compounds induced slight increases in QT and PR intervals. This was not surprising due to the fall in heart rate. However, no increase in QTc was detected with either almotriptan or sumatriptan (Fig. 4).

4. Discussion

The results reported here demonstrate that almotriptan has a favourable cardiovascular safety profile in six animal models.

Almotriptan (10 μM) did not modify cardiac performance in isolated guinea pig hearts. This concentration of almotriptan was 50 times higher than the human plasma levels ($C_{max} \approx 150$ nM) reached following oral administration of the therapeutic dose (12.5 mg) (Cabarrocas and Salvà, 1997).

Regarding the effects of almotriptan and sumatriptan (both at 60 mg/kg, p.o.) in telemetered normotensive Wistar rats, even though the expected plasma levels for both compounds in the present study were higher than those necessary to produce an increase in blood pressure in humans (MacIntyre et al., 1992; Cabarrocas and Salvà, 1997) none of these compounds affected blood pressure or heart rate.

In the open-chest anaesthetised beagle dog model, almotriptan tended to increase total peripheral resistance at high doses, to an extent similar to that described for sumatriptan (Feniuk et al., 1989), but far less so than reported for ergotamine in dogs and cats (Saxena and Vlaam-Schluter, 1974; Johnston and Saxena, 1978). In contrast to almotriptan, sumatriptan induced a cardiodepressant effect (mainly fall in heart rate and dP/dt_{max}). The meaning of these effects is unclear. The bradycardiac effect of sumatriptan has been attributed to an effect on the central nervous system (Coote et al., 1987) and has also been observed in pigs (Den Boer et al., 1991).

The study of coronary blood flow in conscious beagle dogs demonstrated that almotriptan had no effect on the cardiovascular parameters evaluated, whereas sumatriptan tended to affect haemodynamic parameters, including producing a trend towards an increased coronary flow. The effect on coronary circulation may have been due to an increased heart rate rather than to a direct effect of the drug. The vasoconstrictor effects of sumatriptan on the coronary arteries of beagle dogs, clearly observed in vitro (Parsons et al., 1992), require doses higher than those used in the present study. Neither almotriptan nor sumatriptan decreased coronary flow or increased vascular resistance at doses of up to 0.3 mg/kg i.v. Almotriptan produced no changes in the ECG intervals evaluated.

In conscious cynomolgus monkeys, doses of 1 mg/kg s.c. of almotriptan had no effect on cardiovascular parameters. Sumatriptan increased blood pressure and heart rate, and decreased the QA interval at this dose; these effects

being slight and transitory. At 3 mg/kg, both compounds produced slight transitory cardiovascular effects, but no morphological ECG alterations. The absence of effects of sumatriptan on the ECG and on the main haemodynamic parameters in cynomolgus monkeys at doses of up to 1 mg/kg i.v. has been reported previously (Humphrey et al., 1991). In our experiment, however, sumatriptan at the subcutaneous dose of 3 mg/kg produced slight but clear haemodynamic effects.

The dog intracoronary infusion model has proven useful to detect ECG alterations (such as torsade de pointes) (Gras et al., 1996). Administering compounds directly into the heart via a coronary artery avoids possible first-pass metabolism, ensuring that higher levels of the parent compound are achieved in myocardial tissue, so this model can also be useful to determine whether such compounds influence cardiac dynamics.

The results reported here suggest that almotriptan has a safe cardiovascular profile. Furthermore, our results are consistent with those of clinical studies in which almotriptan at the recommended therapeutic dose (12.5 mg) has the same incidence of cardiovascular adverse events as does the placebo (Robert et al., 1999).

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