The effect of rizatriptan, ergotamine, and their combination on human peripheral arteries: a double-blind, placebo-controlled, crossover study in normal subjects

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Aims To compare the peripheral vasoconstrictor effects of ergotamine, rizatriptan, and their combination, in normal subjects.

Methods This was a double-blind, four-way, crossover study. Sixteen young male volunteers, selected as responders to the vasoconstrictor effect of 0.5 mg ergotamine i.v., were administered 10 mg oral rizatriptan, 0.25 mg i.v. ergotamine, 10 mg oral rizatriptan + 0.25 mg i.v. ergotamine, and placebo. The vasoconstrictor effect on peripheral arteries was measured with strain gauge plethysmography up to 8 h after dosing. The 8 h assessment period was divided into two 4 h intervals to assess the immediate (0–4 h) *vs* sustained effect (4–8 h) of treatment.

Results For the 0–4 h interval, the decreases in peripheral systolic blood pressure gradients were: placebo (–1 mmHg [95% CI: –3, 1]) < rizatriptan (–5 mmHg [95% CI: –7, –3]) < ergotamine (–15 mmHg [95% CI: –16, –13]) = rizatriptan + ergotamine (–15 mmHg [95% CI: –17, –13]). For the 4–8 h interval, the decreases were: placebo (–5 mmHg [95% CI: –8, –3]) = rizatriptan (–8 mmHg [95% CI: –11, –5]) < ergotamine (–26 mmHg [95% CI: –29, –24]) = rizatriptan + ergotamine (–28 mmHg [95% CI: –31, –26]).

Conclusions In normal subjects, rizatriptan 10 mg orally had only a small transient vasoconstrictor effect on peripheral arteries compared with the sustained and more pronounced effect of 0.25 mg i.v. ergotamine. Furthermore, rizatriptan exerted no additional effect on ergotamine-induced constriction of peripheral arteries when the two drugs were given in combination.

Keywords: ergotamine, migraine, peripheral arteries, rizatriptan

Introduction

The novel selective 5-HT_{1B/1D} receptor agonists (triptans) sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, and eletriptan, are highly effective for the acute treatment of migraine [1, 2]. The effects of the triptans may be partly attributed to their vasoconstrictor effect on dilated cerebral vessels mediated by the 5HT_{1B} receptor [3, 4]. Although the triptans are targeted at cerebral vessels [5, 6], 5HT_{1B} receptors are also present in lower density

on peripheral vessels [7–10], raising the possibility of peripheral vascular side-effects [11].

Ergotamine is an older drug which has been widely used in the treatment of migraine [12, 13]. In addition to 5-HT_{1B/1D} agonistic activity, ergotamine has high affinity for a wide range of receptors [12]. Its clinical use is hampered by stimulation of dopamine D₂ receptors causing nausea [12, 14] and 5-HT₂ receptors causing a long-lasting (≥ 24 h) constriction of peripheral arteries in man [12, 15].

In vitro, sumatriptan causes constriction of small subcutaneous arteries [7], and, in man, subcutaneous sumatriptan (8 mg) causes a short-lasting minor constriction of leg arteries as measured with strain gauge plethysmography [16]. Zolmitriptan in a very high oral dose of 20 mg, eight times the therapeutic dose of 2.5 mg,

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results in a moderate constriction of leg arteries [17]. The constrictor effects of sumatriptan and zolmitriptan were additive to the effect of coadministered ergotamine [16, 17].

In randomized clinical trials, rizatriptan has proved to be highly effective in the acute treatment of migraine, with 10 mg representing the optimal dose [1, 2]. The aim of the present study, which was conducted as part of the Phase I development programme for rizatriptan, was to investigate the amount and duration of a possible peripheral vasoconstrictor effect of this clinically used dose of rizatriptan, by comparing it with the well characterized effect of ergotamine given i.v. in normal subjects [18]. In addition, the effect of coadministering these two drugs was also investigated. Although contraindicated in the product label, it is possible that some patients may coadminister ergotamine and rizatriptan to treat a migraine attack and it was therefore important to determine whether the two agents had additive effects.

Methods

Ergotamine screen

Twenty-five healthy, male, nonsmoking (for at least 1 year), volunteers were screened for responsiveness to ergotamine. Subjects were screened to exclude the possibility of any form of ischaemic disease. Ergotamine tartrate (Ergotamin DAK) 0.5 mg was administered intravenously over 5 min. The subjects were monitored by strain gauge plethysmography for determination of toe-arm systolic blood pressure (SBP) gradients (see below). Subjects qualified for entry into the four-period crossover study if they displayed a decrease of the toe-arm SBP gradient of >25 mmHg, 4–6 h postdose.

Measurement of toe-arm SBP gradients

Strain gauge plethysmographic measurement of SBP is a noninvasive method of blood pressure measurement [18]. A blood pressure cuff is placed on the measuring site and a very sensitive mercury-in-silastic strain gauge volume indicator (DIGIMATIC DM2000, Medimatic Inc., Copenhagen, Denmark) is placed distally to the cuff. The cuff is rapidly inflated to suprasystolic pressure and, as the pressure is gradually reduced, the first reappearance of arterial pulsations indicates SBP.

Four-period crossover study

Seventeen subjects aged between 21 and 34 years (mean = 25.5 years), and weighing between 66.2 and 87 kg (mean = 74.2 kg), completed the screen and entered the main study. One subject left the study after only one

period due to a knee sprain not related to the study medication (see 'Results'). Sixteen subjects completed all four periods. Subjects received each of the following four treatments in a balanced, randomized, double-blind, crossover fashion: oral rizatriptan 10 mg plus placebo i.v.; oral placebo plus 0.25 mg ergotamine tartrate i.v.; oral rizatriptan 10 mg plus 0.25 mg ergotamine tartrate i.v.; oral placebo plus placebo i.v. Oral treatment (rizatriptan 10 mg or placebo) was administered first with 150 ml of water, followed immediately by i.v. treatment (ergotamine 0.25 mg or saline placebo). The effect on peripheral SBP was measured by determination of the toe-arm SBP gradients until 8 h postdose. There was a washout period of 5–10 days between consecutive treatment days.

On each study day, subjects reported to the clinic for each treatment period having fasted overnight. Subjects were rested supine and continued to fast until 4 h postdose, at which time they were served a standard lunch. The hand and arm were supported at heart level and the strain gauges left *in situ* for the rest of the study day. Toe and arm SBP measurements were made simultaneously [18]. The left toe-left arm measurements were performed first, in triplicate, then the right toe-left arm measurements were performed, in triplicate. The arm SBP served as a reference; for each set of toe-arm SBP measurements, the toe-arm SBP gradient was calculated (toe SBP minus simultaneous arm SBP). The mean value of the six toe-arm SBP gradients at each time point was considered the value for that time point. Toe-arm SBP gradients were assessed predose (twice at –15 min and 0 min); every 15 min until 30 min postdose; every 30 min until 4 h postdose; and then every 1 h until 8 h postdose. Toe temperatures were manipulated (by blankets on and off) to keep them as close as possible to those measured at baseline for each experiment. ECG was monitored continuously from baseline to 4 h postdose and heart rate was recorded at the same time intervals as SBP measurements up to 4 h postdose. Any adverse events occurring during the study were also recorded.

Ethics

Subjects gave informed consent after being provided with oral and written information. The study was approved by the Ethics Committee of Copenhagen.

Statistical analysis

The primary hypotheses of this study were: (1) rizatriptan would produce less peripheral vasoconstriction than ergotamine as measured by changes from baseline in toe-arm SBP gradients over the 0–4 h and 4–8 h post-treatment time intervals; (2) the combination of rizatriptan

and ergotamine would generate changes from baseline in toe-arm SBP gradients that were not greater than additive. The 8 h assessment period was divided into two 4 h intervals to assess the immediate (0–4 h) *vs* sustained effect (4–8 h) of treatment. The mean changes from baseline in toe-arm SBP gradients for the 0–4 h and 4–8 h intervals were divided by the length of time and number of assessments within intervals and thus represent time interval weighted averages. This method of data summary takes account of the unequal spacing of measurements, and missing observations for each subject.

Based upon a sample size of 16 subjects, the study provided 80% power (at $\alpha=0.05$, two tailed) to detect a within-treatment mean change from baseline of 3.5 mmHg in toe-arm SBP; a between-treatment mean change of 4.6 mmHg would also be detected. This calculation was based upon an estimated pooled between subject standard deviation of 4.5 mmHg for SBP gradient [Tfelt-Hansen, personal observation].

Analysis of variance (ANOVA) for a four-period crossover design was used to assess the effect of each treatment regimen on mean gradient as defined by the above summary measures. The ANOVA model included terms for subject, treatment, period, and carryover. For each of the summary measures, the carryover effect was found to be not significant ($P>0.200$) and was dropped from the ANOVA model. The ANOVA model assumptions were satisfied on the raw data and corroborated by the ranks of the raw data; thus all *P* value results are based upon the raw data analyses. The additivity hypothesis, that the combination of rizatriptan + ergotamine would produce effects that were not greater than the sum of the effects of the rizatriptan and ergotamine monotherapies, was tested using a linear contrast statement from PROC GLM in SAS. All tests of significance were performed at $\alpha=0.05$, two-tailed. The subject who discontinued after one treatment period was excluded from the analysis of toe-arm SBP gradients.

In addition to the toe-arm SBP analysis, the heart rate-SBP product was calculated at each time point up to 4 h as a measure of change in cardiac work. Plots of the data were

examined visually for any changes associated with the treatment, but the data were not formally analysed.

Results

Baseline SBP and heart rate

There were no relevant differences at baseline between treatment groups with regard to SBP or heart rate (Table 1).

Toe-arm SBP gradients

The primary endpoint for the study was weighted mean change from baseline in toe-arm SBP gradients over the time intervals of 0–4 h and 4–8 h post-treatment (Table 2).

0–4 h interval

The weighted mean changes from baseline in SBP gradient across the 0–4 h interval were -5.1 mmHg for rizatriptan (95% CI: -7.0 , -3.1), -14.6 mmHg for ergotamine (95% CI: -16.5 , -12.6), -15.1 mmHg for rizatriptan + ergotamine (95% CI: -17.0 , -13.2), and -1.0 mmHg for placebo (95% CI: -3.0 , 0.9) (Figure 1). Rizatriptan, ergotamine, and the combination of rizatriptan + ergotamine produced a significant reduction in peripheral SBP gradients when compared to placebo (rizatriptan *vs* placebo difference = -4.0 mmHg [95% CI: -6.7 , -1.3], $P=0.005$; ergotamine *vs* placebo difference = -13.5 mmHg [95% CI: -16.3 , -10.8], $P<0.001$; rizatriptan + ergotamine *vs* placebo difference = -14.1 mmHg [95% CI: -16.8 , -11.3], $P<0.001$). Rizatriptan produced much less decrease in mean SBP gradients than did ergotamine (difference = 9.5 mmHg [95% CI: 6.8 , 12.2], $P<0.001$). No significant difference was found between ergotamine and the rizatriptan + ergotamine combination (difference = 0.5 mmHg [95% CI: -2.2 , 3.2], $P=0.701$). The effect of the combination treatment of

Table 1 Mean SBPs and heart rate at baseline.

Measurement	Rizatriptan 10 mg p.o. (n = 16)	Ergotamine 0.25 mg i.v. (n = 16)	Rizatriptan 10 mg p.o. + ergotamine 0.25 mg i.v. (n = 16)	Placebo (n = 16)
<i>Left toe-left arm</i>				
Left arm SBP	113	112	112	112
Left toe SBP	105	103	103	105
<i>Left toe-right arm</i>				
Left arm SBP	114	113	112	113
Right toe SBP	103	104	102	105
Heart rate (beats min ⁻¹)	59	57	57	57

Table 2 Weighted change from baseline in mean toe-arm SBP gradient (mmHg) and results of statistical testing.

Treatment	n	Mean (s.d.)	Treatment 1 vs treatments 2, 3, 4	Treatment 2 vs treatments 3, 4	Treatment 3 vs treatment 4
<i>0–4 h</i>					
1. Rizatriptan 10 mg p.o.	16	−5.1 (3.8)	–	–	–
2. Ergotamine 0.25 mg i.v.	16	−14.6 (5.8)	$P < 0.001$	–	–
3. Rizatriptan 10 mg p.o. + ergotamine 0.25 mg i.v.	16	−15.1 (5.8)	$P < 0.001$	$P = 0.701$	–
4. Placebo	16	−1.0 (2.1)	$P = 0.005$	$P < 0.001$	$P < 0.001$
<i>4–8 h</i>					
1. Rizatriptan 10 mg p.o.	16	−8.0 (4.0)	–	–	–
2. Ergotamine 0.25 mg i.v.	16	−26.3 (7.1)	$P < 0.001$	–	–
3. Rizatriptan 10 mg p.o. + ergotamine 0.25 mg i.v.	16	−28.2 (8.5)	$P < 0.001$	$P = 0.299$	–
4. Placebo	16	−5.2 (5.4)	$P = 0.125$	$P < 0.001$	$P < 0.001$

s.d. = between subject standard deviation.

Figure 1 Mean change from baseline in toe-arm SBP gradient (mmHg). ▲ = rizatriptan 10 mg p.o., ● = placebo, □ = ergotamine 0.25 mg i.v., ○ = rizatriptan 10 mg p.o. + ergotamine 0.25 mg i.v. Vertical bars show $\pm$ the between subject s.d.

rizatriptan + ergotamine tended to be less than the additive effects of the rizatriptan and ergotamine monotherapies, and this difference approached statistical significance (difference = 3.5 mmHg [95% CI: −0.3, 7.3], $P = 0.073$).

4–8 h interval

The weighted mean changes from baseline in SBP gradients across the 4–8 h interval were −8.0 mmHg for rizatriptan (95% CI: −10.5, −5.5), −26.3 mmHg for ergotamine (95% CI: −28.9, −23.8), −28.2 mmHg for rizatriptan + ergotamine (95% CI: −30.7, −25.7), and −5.2 mmHg for placebo (95% CI: −7.8, −2.7). Whereas the difference between the rizatriptan and placebo treatments was not significant (difference = −2.8 mmHg [95% CI: −6.4, 0.8], $P = 0.125$), ergotamine alone or in combination with rizatriptan produced a significant reduction in mean SBP gradient

(ergotamine *vs* placebo difference = −21.1 mmHg [95% CI: −24.7, −17.5], $P < 0.001$; rizatriptan + ergotamine *vs* placebo difference = −23.0 mmHg [95% CI: −26.5, −19.4], $P < 0.001$). The difference between ergotamine alone and the combination treatment was not significant (difference = 1.9 mmHg [95% CI: −1.7, 5.5], $P = 0.299$). The comparison of the combination treatment of rizatriptan + ergotamine *vs* the additive effects of the rizatriptan and ergotamine monotherapies was non significant (difference = 0.9 mmHg [95% CI: −4.2, 6.0], $P = 0.720$).

Heart rate-SBP product

The heart rate-SBP product was calculated as a measure of changes in cardiac work associated with treatments. The

Table 3 Clinical adverse events.

	Rizatriptan 10 mg p.o. (n = 16)	Ergotamine 0.25 mg i.v. (n = 16)	Rizatriptan 10 mg p.o. + ergotamine 0.25 mg i.v. (n = 16)	Placebo (n = 17)
Number of subjects with adverse event	5	16	14	7
<i>Type of adverse event</i>				
Nausea	—	14	11	—
Vomiting	—	2	1	—
Malaise	—	5	5	1
Sweating	—	5	5	—
Dizziness	—	1	2	2
Drowsiness	2	2	1	1
Warm sensation	—	3	2	—
Pressure sensation	—	3	4	—
Chest symptoms	—	2	3	—
Headache	2	2	3	6
Paresthesia	1	3	3	1
Restlessness	—	1	2	—
Throat symptoms	—	2	3	1
Others	—	5	3	1

product was increased transiently (for approximately 1 h after dosing) by ergotamine but not by rizatriptan (data not shown).

Tolerability

Adverse events occurred in 5 of 16 subjects (31%) given rizatriptan and in 7 of 17 subjects (41%) given placebo (Table 3). After ergotamine, adverse events occurred in 16 out of 16 subjects (100%). After rizatriptan + ergotamine, 14 of 16 subjects (88%) experienced an adverse event (Table 2). There was thus a 69% (95% CI: 46%, 91%) greater incidence of adverse events after ergotamine than after rizatriptan, and a 56% (95% CI: +28% to +84%) greater incidence after rizatriptan + ergotamine than after rizatriptan alone. The most common adverse event was mild to severe nausea which was observed in 14 of 16 subjects given ergotamine (two of these subjects also vomited) and in 11 of 16 subjects given rizatriptan + ergotamine (one of these subjects also vomited). Mild to moderate chest pain was observed in three subjects; in two subjects after both ergotamine and rizatriptan + ergotamine, and in one subject only after rizatriptan + ergotamine. The chest pain was not associated with any ischaemic ECG changes. One subject was discontinued due to a clinical adverse event that was considered definitely not related to the study medication; the subject experienced a knee injury 6 days after period 1 (placebo), had a cast placed on his leg, and could no longer participate in the study. There were no laboratory adverse events attributed to rizatriptan, ergotamine, or rizatriptan + ergotamine, and no significant ECG changes.

Discussion

The strain gauge plethysmographic measurement of peripheral SBP used in this study has been useful in quantifying the vasoconstrictor effect of ergotamine on leg arteries in man [18–20]. In the presence of an agent that acts as a peripheral arterial vasoconstrictor, SBP measured at distal sites is diminished because of constriction of the conducting arteries and the consequent decreased pulse amplitude distally [18]. SBP in the more central arteries (e.g. the arm) is less affected by arterial vasoconstrictors and serves as a reference point and control for changes in systemic blood pressure that may be caused by other factors [18]. A decrease in toe-arm SBP gradient (toe SBP minus arm SBP) corresponds to a constriction of the leg arteries.

Since subjects vary considerably in their sensitivity to an i.v. dose of 0.5 mg ergotamine, with decreases in toe-arm SBP gradients from 1 to –56 mmHg in migraine patients [15, 20], and from –8 to –46 mmHg in normal volunteers [19], the subjects in this study were first challenged with this maximum i.v. dose of ergotamine to select those with a pronounced reaction to a vasoconstrictor drug.

The first primary hypothesis of this study was that rizatriptan would produce less peripheral vasoconstriction than ergotamine in normal subjects as measured by changes (decreases) from baseline in toe-arm SBP. In both the 0–4 h and the 4–8 h post-treatment intervals, the decrease in toe-arm SBP gradients were less for rizatriptan 10 mg orally than for i.v. ergotamine 0.25 mg. The results for 0.25 mg ergotamine i.v., a dose not in general use in acute migraine treatment but used in the treatment of cluster headache attacks [Tfelt-Hansen, personal

observation], are in the same range as found previously in volunteers [16, 19]. The effect of the therapeutically used dose of 10 mg oral rizatriptan was in the same range as the transient (≤ 4 h) effect of 8 mg subcutaneous sumatriptan [16], and approximately half the effect of 20 mg oral zolmitriptan [17], a dose eight times the recommended 2.5 mg dose of zolmitriptan. A dose of 0.25 mg i.v. ergotamine therefore produces a more pronounced constriction of leg arteries than triptans. This is most likely not just a question of the magnitude of the dose of ergotamine given since a very low dose of 1 mg rectal ergotamine resulted in a decrease in toe-arm SBP gradient of approximately -10 mmHg [21]. Ergotamine thus probably causes more peripheral vasoconstriction than the triptans.

As shown in Figure 1 and Table 2, another important fundamental difference between rizatriptan and ergotamine is that whereas the effect of rizatriptan was only different from placebo for the first 4 h, the effect of ergotamine was different from placebo for both time intervals and was sustained for the 8 h observation period. The same was the case for the rizatriptan + ergotamine combination (Figure 1 and Table 2). Thus rizatriptan, like sumatriptan [16], appears to have only a short lived effect on large peripheral arteries, in contrast to ergotamine where an effect can be observed the next day [15, 18, 20, 22]. Rizatriptan, sumatriptan, and ergotamine have similar plasma half-lives of 2 h [2, 12, 22]. The longer duration of vasoconstriction for ergotamine is most likely due to the tight binding of this drug to the vascular receptors [2].

The minor effect of rizatriptan on peripheral arteries in man is theoretically interesting because, together with previous results on sumatriptan [16] and zolmitriptan [17] using strain gauge plethysmography, and recent results with ultrasound showing a decrease of approximately 10% of the diameter of the brachial artery after therapeutic oral doses of sumatriptan, zolmitriptan, and rizatriptan [11], it confirms the presence of 5-HT_{1B} receptors on the large peripheral arteries in man. Similarly, it was found that sumatriptan contracts small subcutaneous arteries *in vitro* [7], and coronary arteries *in vivo* [23]. Thus, the 5-HT_{1B} receptor appears to be present on the arteries throughout the human body, but in most *in vivo* studies [11, 16, 17, 23] activation of these receptors results in only minor constriction of the arteries.

It is possible that migraine patients may coadminister rizatriptan and ergotamine during a migraine attack although this is not recommended [24]. We therefore also evaluated the effect of the combination compared with that of the two individual drugs. It was hypothesized that the combination of rizatriptan and ergotamine would generate changes from baseline in toe-arm SBP gradients that would not be greater than additive. Additive effects have previously been reported for 8 mg

subcutaneous sumatriptan + 0.25 mg ergotamine i.v. [16], and a high dose of 20 mg oral zolmitriptan + 2 mg oral ergotamine [17]. In contrast, in this study, oral rizatriptan 10 mg + ergotamine 0.25 mg i.v. caused decreases in toe-arm SBP gradients that were not different from those produced by ergotamine alone. The reason for this apparent difference among the three triptans, sumatriptan, zolmitriptan, and rizatriptan, remains unclear but could reflect the route of administration or doses studied.

In randomized clinical trials in migraine, rizatriptan 10 mg causes a 17% (95% CI: 12%, 22%) higher incidence of adverse events than placebo [1, 2], but in this study in healthy young subjects the incidence of adverse events after rizatriptan was similar to the incidence after placebo. In contrast, ergotamine 0.25 mg i.v. caused adverse events in all subjects and, as in migraine patients [15], nausea was the most common adverse event.

The constrictor effect of 10 mg rizatriptan on leg arteries in man in the present study was so minimal and transient that it was hardly clinically relevant. Since there was no additive effect of rizatriptan and ergotamine, the question arises as to whether these two drugs can be taken concomitantly or consecutively in the treatment of a migraine attack. Based on the results of the present study in normal subjects, there should be no more peripheral vasoconstrictor side-effects if rizatriptan and ergotamine are given together than after ergotamine alone. However, extrapolating results from normal subjects to patients may be misleading because it is possible that patients may differ with regard to their vascular sensitivity [25]. In any case, the real clinical problem is safety and not tolerability. Myocardial infarction after use of ergotamine has been reported [26], and sumatriptan has been associated with rare cases of myocardial ischaemia [1, 27]. Based on *in vitro* studies [28], all triptans have the potential for inducing coronary vasospasms, and it is currently not known whether the combination of ergotamine and a triptan may have additive effects on the coronary arteries in some individuals. (It should be emphasized that the subjects in this study were all normal healthy individuals who were screened to ensure that they were not suffering from ischaemic disease.) Therefore, simultaneous administration of a triptan and ergotamine should be avoided.

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