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Coronary Side-Effect Potential of Current and Prospective Antimigraine Drugs

Antoinette MaassenVanDenBrink, MSc; Marije Reekers, MSc; Willem A. Bax, MD, PhD;
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Background—The antimigraine drugs ergotamine and sumatriptan may cause angina-like symptoms, possibly resulting from coronary artery constriction. We compared the coronary vasoconstrictor potential of a number of current and prospective antimigraine drugs (ergotamine, dihydroergotamine, methysergide and its metabolite methylergometrine, sumatriptan, naratriptan, zolmitriptan, rizatriptan, avitriptan).

Methods and Results—Concentration-response curves to the antimigraine drugs were constructed in human isolated coronary artery segments to obtain the maximum contractile response (E_{max}) and the concentration eliciting 50% of E_{max} (EC_{50}). The EC_{50} values were related to maximum plasma concentrations (C_{max}) reported in patients, obtaining C_{max}/EC_{50} ratios as an index of coronary vasoconstriction occurring in the clinical setting. Furthermore, we studied the duration of contractile responses after washout of the acutely acting antimigraine drugs to assess their disappearance from the receptor biophase. Compared with sumatriptan, all drugs were more potent (lower EC_{50} values) in contracting the coronary artery but had similar efficacies (E_{max} <25% of K^+-induced contraction). The C_{max} of avitriptan was 7- to 11-fold higher than its EC_{50} value, whereas those of the other drugs were <40% of their respective EC_{50} values. The contractile responses to ergotamine and dihydroergotamine persisted even after repeated washings, but those to the other drugs declined rapidly after washing.

Conclusions—All current and prospective antimigraine drugs contract the human coronary artery in vitro, but in view of low efficacy, these drugs are unlikely to cause myocardial ischemia at therapeutic plasma concentrations in healthy subjects. In patients with coronary artery disease, however, these drugs must remain contraindicated. The sustained contraction by ergotamine and dihydroergotamine seems to be an important disadvantage compared with sumatriptan-like drugs. (***Circulation***. 1998;98:25-30.)

Key Words: coronary disease ∎ vasoconstriction ∎ migraine ∎ pharmacology ∎ antimigraine drugs

Sumatriptan, a 5-HT derivative with agonist activity at $5\text{-HT}_{1B/1D}$ receptors, is highly effective in aborting attacks of migraine and cluster headache. The drug is generally well tolerated. However, up to 15% of patients consistently report chest symptoms, including chest pressure, tightness, and pain, often mimicking angina pectoris.[1–3] Although extracardiac mechanisms have been invoked,[4] chest symptoms may well be caused by coronary vasoconstriction, which has been observed after sumatriptan both in vivo[5] and in vitro.[6–8] In some cases, the use of sumatriptan, like that of ergotamine,[9–11] was even associated with myocardial infarction[12,13] and cardiac arrest.[14] "Second-generation" sumatriptan-like antimigraine drugs are all aimed at, in addition to achieving high efficacy and long duration of action, avoiding coronary vasoconstrictor activity.[15]

The present study deals with 2 major issues in clinical practice: (1) Do new antimigraine compounds cause less coronary artery constriction than sumatriptan? and (2) Is sumatriptan better than ergot derivatives in this respect? Obviously, these questions cannot be easily answered by clinical trials. We therefore employed a pharmacological approach using the human isolated coronary artery to determine the potency (sensitivity) and efficacy (magnitude) of the contractile responses to sumatriptan and other current (ergotamine, dihydroergotamine, methysergide, and its active metabolite methylergometrine[16]) as well as new (naratriptan,[17] zolmitriptan,[18,19] rizatriptan,[20] and avitriptan[21]) antimigraine drugs. Results were related to the respective C_{max} reported in patients.

Because sumatriptan-induced contractions of coronary arteries show substantial variability both within and between studies,[22,23] we used a "parallel" experimental design involving segments from the same coronary artery. These coronary arteries were obtained from organ donors who died of causes unrelated to cardiac diseases and therefore may potentially represent the population treated with antimigraine drugs.

Methods

Preparation of Tissue

Right epicardial coronary arteries were obtained from 14 "heart beating" organ donors (7 male, 7 female; age, 7 to 61 years) who died of noncardiac disorders (11 of cerebrovascular accident, 3 of

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Selected Abbreviations and Acronyms

C_{max} = maximum plasma concentrations
EC_{50} = concentration eliciting 50% of its own E_{max}
E_{max} = maximum effect, maximum contraction
5-HT = 5-hydroxytryptamine
$PGF_{2\alpha}$ = prostaglandin $F_{2\alpha}$

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head trauma) <24 hours before the tissue was taken to the laboratory. Hearts were provided by the Rotterdam Heart Valve Bank (Bio Implant Services/Eurotransplant Foundation) after removal of the aortic and pulmonary valves for transplantation purposes. The study was approved by the joint Ethical Committee of the Erasmus University Rotterdam and the University Hospital Rotterdam "Dijkzigt." The hearts were stored at 0°C to 4°C in a sterile organ-protecting solution immediately after circulatory arrest. After arrival in the laboratory, the right coronary artery was removed and placed in a cold, oxygenated Krebs bicarbonate solution of the following composition (mmol/L): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_2$ 25, and glucose 8.3; pH 7.4. Vessels were cut into rings ≈4 mm long, suspended on stainless steel hooks in 15-mL organ baths containing Krebs bicarbonate solution, aerated with 95% O_2/5% CO_2, and maintained at 37°C. Vessel segments containing distinct, macroscopically visible atherosclerotic lesions were not used.

Experimental Protocol

After equilibration for at least 30 minutes and a wash every 15 minutes, changes in tissue force were recorded with a Harvard isometric transducer. The vessel segments, stretched to a stable force of ≈15 mN, were exposed to 30 mmol/L K^+ twice, and the functional integrity of the endothelium was verified by observation of relaxation to substance P (1 nmol/L) after precontraction with $PGF_{2\alpha}$ (1 μmol/L). The tissue was washed and then exposed to 100 mmol/L K^+. The data obtained with $PGF_{2\alpha}$, substance P, and 100 mmol/L K^+ were averaged for each coronary artery. Subsequently, the vessel segments were washed again and, after a 30-minute equilibration period, 2 series of experiments were performed.

Concentration-Response Curves and Relation With Clinical Plasma Concentrations

In the first series of 9 experiments, a concentration-response curve was constructed with the different compounds (ergotamine, dihydro-

ergotamine, methysergide, methylergometrine, sumatriptan, naratriptan, rizatriptan, avitriptan, and zolmitriptan, as well as 5-HT used as a marker). In some cases, concentration-response curves to sumatriptan were obtained in duplicate, which were averaged and regarded as one curve in further analysis. As described earlier in detail,[23] contractile responses were expressed as a percentage of the contraction induced by 100 mmol/L K^+ in the respective segments, and the data were analyzed to obtain, in each case, values of E_{max} and EC_{50}. The E_{max} and EC_{50} values represent the efficacy and potency, respectively, of a drug in eliciting a response (in this case, coronary artery contraction). Thus, the lower the EC_{50} of a drug, the more likely it is to cause coronary vasoconstriction at lower plasma concentrations; the E_{max} is obviously only of importance when a drug is present in high enough concentrations, as dictated by its potency. To assess the capacity of various agonists to contract the human coronary artery during clinical use in migraine, we calculated the ratio between the reported C_{max} after administration of clinically effective doses (Table) and the EC_{50} value of the compounds in contracting the human isolated coronary artery. Thus, a high C_{max}/EC_{50} ratio indicates that the plasma concentration of the drug is high enough to contract the human coronary artery in the clinical situation. The magnitude of this contraction will be dictated by the E_{max} of the drug.

Duration of Action

In a second series of 5 experiments, the durations of action of the acutely acting antimigraine drugs (ergotamine, dihydroergotamine, sumatriptan, naratriptan, rizatriptan, avitriptan, and zolmitriptan) were compared. For this purpose, contractions of coronary artery segments were elicited with a single concentration of these drugs (2 times EC_{50}, as determined in the first series of experiments), and the time to reach a stable contraction was noted. The segments were then washed twice every 15 minutes, and contractions remaining after each wash were noted for a total period of 90 minutes.

Analysis of Data

Differences between EC_{50} and E_{max} values of sumatriptan and other compounds as well as between contractions remaining after each wash (every 15 minutes) were evaluated with Duncan's new multiple range test, once an ANOVA (randomized block design) had revealed that the samples represented different populations. The E_{max} of the compounds tested was correlated with the relaxant response to substance P obtained in the individual coronary arteries (Pearson's

E_{max} (Expressed as % of Effect Caused by 100 mmol/L K^+) and EC_{50} (nmol/L) Values in Human Isolated Coronary Artery of 5-HT and Antimigraine Drugs, Together With Their Therapeutic Doses and C_{max} in Patients

	EC_{50}, nmol/L	E_{max}, %K^+	Dose, mg, and Mode of Administration	C_{max}, nmol/L
5-HT	334±99*	58.3±7.9*	...	...
Sumatriptan	803±197	14.0±2.9	100 PO[2,42]	142–183[2,42]
			6 SC[2,42]	244–261[2,42]
Naratriptan	171±36*	10.1±2.1	2.5, 5 PO[43]	38, 71[43]
Rizatriptan	448±88*	10.1±2.7	10 PO[44,45]	74–93[45]
Zolmitriptan	476±87*	11.8±2.5	2.5, 5 PO[18,46]	9, 17[18]
Avitriptan	89±16*	7.7±1.8	75, 150 PO[21]	628, 948[21]
Ergotamine	17±7*	20.5±3.7	2 PO	0.03–0.62[47,48]
			0.5 IM[47]	1.38–3.27[47]
Dihydroergotamine	20±10*	13.0±2.5	0.75, 1 IM/SC[49]	3, 4[49]
Methysergide†	243±98*	7.8±1.9	2 PO[16]	5[16]
Methylergometrine†	46±14*	13.4±3.5	2 methysergide PO[16]	14[16]

*Significantly different from sumatriptan (P<0.05).
†Not used in acute migraine therapy.
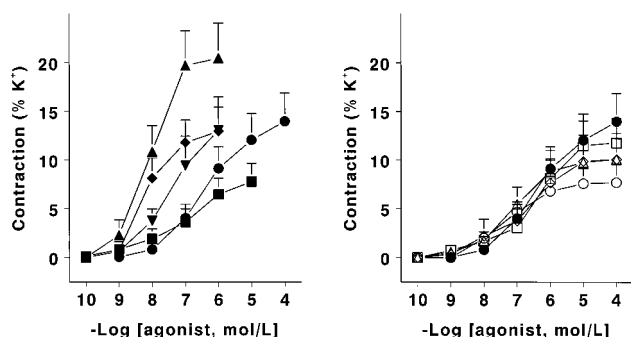
Figure 1. Concentration-response (expressed as % of response to 100 mmol/L K$^+$) curves in human isolated coronary arteries (n=9) obtained with current (left: ergotamine, ▲; dihydroergotamine, ♦; methysergide, ■; and its metabolite methylergometrine, ▼) and potential (right: zolmitriptan, □; rizatriptan, ◇; naratriptan, △; and avitriptan, ○) antimigraine drugs compared with sumatriptan (●). Data are mean±SEM.

correlation coefficient). Values of $P \leq 0.05$ were considered to indicate significant differences. All data in the text and illustrations are presented as mean±SEM.

Results

### Basic Properties of the Preparations: Effects of Substance P and Potassium

All coronary artery segments, obtained from 14 hearts, relaxed after substance P (1 nmol/L), the response amounting to 61±8% of the precontraction (35±2 mN) to PGF$_{2\alpha}$ (1 μmol/L). Contraction to 100 mmol/L KCl was 47±3 mN.

Concentration-Response Curves and Relation With Substance P Response and Clinical Plasma Concentrations

Concentration-response curves obtained in 9 coronary arteries with the various compounds investigated are shown in Figure 1, and the derived values of EC$_{50}$ (nmol/L) and E$_{max}$ (% of contraction elicited by 100 mmol/L K$^+$) are shown in the Table. As reported earlier,[22,23] the contractile effect of sumatriptan on the isolated human coronary artery showed a considerable variability; the EC$_{50}$ and E$_{max}$ values ranged from 117 to 2042 nmol/L and 2.3% to 27.0% of the response to 100 mmol/L K$^+$, respectively. The EC$_{50}$ values of all compounds, in particular ergotamine, dihydroergotamine, and methylergometrine, were significantly lower than that of sumatriptan. The E$_{max}$ of 5-HT was significantly higher, but those of the other compounds did not differ significantly from that of sumatriptan. However, it may be noted that the E$_{max}$ of other triptan derivatives is about half that of ergotamine.

In the 9 hearts in which concentration-response curves to the antimigraine agents were constructed, the correlation between the E$_{max}$ of the drugs and the coronary artery relaxation to substance P (1 nmol/L) after precontraction with PGF$_{2\alpha}$ (1 μmol/L) was assessed. Pearson's correlation coefficient did not yield a significant P value with any of the drugs (data not shown).

Figure 2 depicts the ratio between the reported plasma C$_{max}$ obtained after administration of a clinically effective dose (see Table) and the EC$_{50}$ value of the compounds in
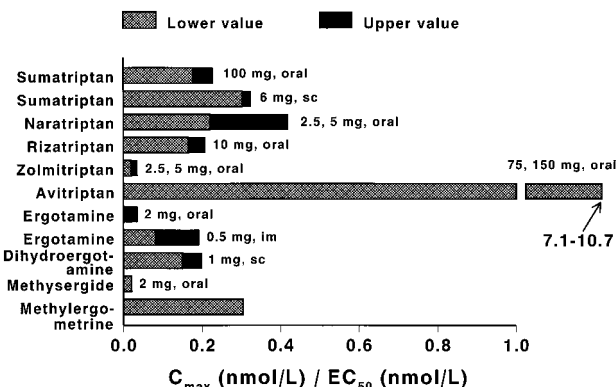
Figure 2. Relationship between reported C$_{max}$ concentration in patients and EC$_{50}$ values of various antimigraine compounds in contracting human isolated coronary artery. Clinical doses and mode of administration associated with C$_{max}$ values (see Table for references) are indicated in each case, except methylergometrine (measured after methysergide, 2 mg PO). When lower and upper values are mentioned, they indicate reported range. Note that a C$_{max}$/EC$_{50}$ ratio of 1 indicates that, if same conditions were applicable in patients as in present in vitro experiments, drug would elicit 50% of its maximum contraction of coronary artery. In view of use of C$_{max}$ data from literature, C$_{max}$/EC$_{50}$ ratios of different drugs were not subjected to statistical analysis.

contracting the human isolated coronary artery. The data show that, compared with that of 100 mg PO sumatriptan, the C$_{max}$/EC$_{50}$ ratios of avitriptan (75 and 150 mg PO) were higher, those of ergotamine (2 mg PO) and zolmitriptan (2.5 and 5 mg PO) were lower, and those of the other compounds (naratriptan, rizatriptan, and methysergide measured as its active metabolite methylergometrine) were in the same range. The ranges of C$_{max}$/EC$_{50}$ ratios obtained with parenteral ergotamine (0.5 mg IM) and dihydroergotamine (1 mg SC) were not much different from that with parenteral sumatriptan (6 mg SC).

Duration of Action

Contractions to a single concentration (2 times EC$_{50}$) of the acutely acting antimigraine drugs were elicited in 5 coronary arteries. The peak stable contraction (% of 100 mmol/L K$^+$) and the time required to reach the peak contraction with the different compounds were as follows: sumatriptan 15±4% (3±2 minutes), naratriptan 10±3% (3±1 minutes), zolmitriptan 21±15% (4±7 minutes), rizatriptan 22±16% (4±2 minutes), avitriptan 17±12% (5±1 minutes), ergotamine 26±7% (24±13 minutes), and dihydroergotamine 27±11% (18±10 minutes). The effects of repeated washings on the peak contractions elicited by each drug are presented in Figure 3. The data show that the contractile responses to ergotamine and dihydroergotamine were sustained over the 90-minute period ($P \leq 0.05$ versus sumatriptan), whereas those to sumatriptan, naratriptan, rizatriptan, avitriptan, and zolmitriptan nearly completely disappeared after the second wash 30 minutes later.

Discussion

Human Coronary Artery Contraction In Vitro

As reported earlier in vitro[6,8,24] and in vivo,[25,26] 5-HT induced contraction of the human isolated coronary artery. 5-HT was
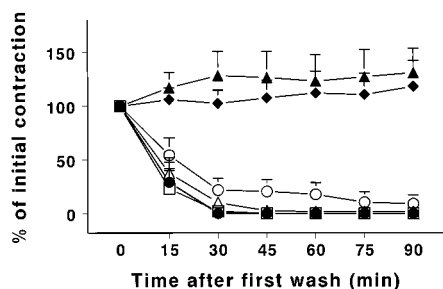
Figure 3. Effect of repeated washings (3 times every 15 minutes) on contractions of human coronary arteries (n=5) elicited by acutely acting antimigraine drugs (ergotamine, ▲; dihydroergotamine, ◆; sumatriptan, ●; zolmitriptan, □; rizatriptan, ◇; naratriptan, △; and avitriptan, ○). All drugs were administered once at a concentration 2 times their EC_{50} (see Table). Data are mean±SEM.

more efficacious (higher E_{max} value) than sumatriptan, because of a more prominent action mediated via $5-HT_2$ receptors.[6,8,24,26]

With respect to the antimigraine compounds, the results of our study show that all drugs, but in particular ergotamine, dihydroergotamine, and methylergometrine (metabolite of methysergide[16]), were more potent (lower EC_{50} values) than sumatriptan in contracting the human isolated coronary artery. Although the E_{max} of ergotamine tended to be somewhat higher than that of sumatriptan, we observed no statistically significant differences between E_{max} values of sumatriptan and any of the other antimigraine drugs. Our findings are in agreement with a recent report on zolmitriptan,[19] but they appear to be at variance with earlier studies claiming that rizatriptan is only half as effective as sumatriptan in contracting the human isolated coronary artery.[27,28] Admittedly, data obtained in human post mortem tissues can vary between experiments because of a variety of factors, which are difficult to discern. However, the coronary arteries used in these studies[27,28] were endothelium-denuded and obtained from hearts from patients undergoing cardiac transplantation. In contrast, the coronary arteries in the present experiments were obtained from organ donors who died of noncardiac causes, and the endothelium was not removed. Thus, our population may better reflect the population likely to be treated with $5-HT_{1B/1D}$ receptor agonists.

Coronary Artery Contraction and Relaxation to Substance P

It is suggested that relaxation to substance P is a measure of the functional integrity of the endothelium and could be related to underlying coronary artery disease.[29,30] Because there was no significant correlation between the E_{max} of the compounds and relaxant response to substance P in the coronary arteries used in the present investigation, it would appear that the contractile effect of the antimigraine drugs is not increased by underlying coronary artery disease. We concede that the present study, with few data points at the outer sides of the range of the relaxant response to substance P, may not be particularly suitable for such an analysis. However, even in a larger analysis (78 donor hearts), we did not find an inverse but rather in fact a positive correlation

between the E_{max} of sumatriptan and the magnitude of substance P relaxation in the human coronary artery.[31]

Coronary Artery Contraction at Therapeutic Plasma Concentrations

We calculated the ratio between the clinically effective plasma C_{max} and EC_{50} values of the different antimigraine compounds to estimate the degree of coronary vasoconstriction to be expected during therapeutic use (see Figure 2). Except for avitriptan, the plasma C_{max} values of all drugs tested remain <40%, and in the case of zolmitriptan, ergotamine (2 mg PO), and methysergide (but note, not its metabolite methylergometrine), even <10% of their EC_{50} values. Thus, with the exception perhaps of avitriptan, therapeutic doses of the antimigraine drugs investigated will cause little coronary artery constriction in vivo. It was recently shown with PET that sumatriptan did not affect myocardial perfusion in healthy migraineurs at therapeutic plasma concentrations.[32] Even in the case of avitriptan, the maximum coronary constriction (E_{max} ≈8% of 100 mmol/L K^+ response) will be barely perceptible and is unlikely to affect coronary artery blood flow, which remains unchanged until the arterial lumen is compromised by >80%.[33] In contrast, in patients with preexisting coronary artery lesions who have only a limited coronary reserve,[33] even a small coronary artery contraction that may occur with plasma concentrations encountered during clinical use could be enough to cause myocardial ischemia. A similar phenomenon may also be observed in patients with "variant" angina pectoris, who have increased coronary artery sensitivity to 5-HT.[26] It has been reported that the contractile effect of sumatriptan on the human isolated coronary artery is potentiated by thromboxane A_2[23,34] and is inhibited by aspirin as well as the thromboxane receptor antagonist SQ30741.[23] Thus, exaggerated production of such substances locally may augment coronary artery contractions to similar antimigraine drugs in vivo.

Additional Factors Involved in Coronary Artery Constriction in Patients

Other factors involved in the contraction of coronary arteries in vivo are slow diffusion from the receptor biophase, plasma protein binding, and the formation of active metabolites. Slow diffusion from the receptor biophase, which has been reported for ergot derivatives,[35] is in accordance with our findings concerning the sustained response to both ergotamine and dihydroergotamine despite repeated washings (Figure 3). In the clinical situation, it is also known that the effects of ergotamine and dihydroergotamine sustain much longer than is to be expected from their plasma concentration profiles.[35–37] Indeed, substernal chest pain and discomfort suggestive of myocardial infarction have repeatedly been described with ergot preparations, particularly ergotamine.[10,38] Dihydroergotamine,[39] methysergide,[16] and possibly ergotamine[38] form active metabolites, which, as is clearly the case with methysergide (see results with methylergometrine), may also cause coronary artery constriction. Sumatriptan does not have active metabolites,[40] but zolmitriptan forms an N-desmethyl derivative, which is approximately twice as

potent as the parent compound in causing vasoconstriction.[41] We do not know whether active metabolites are formed by avitriptan, naratriptan, or rizatriptan. However, in view of its structural similarity to zolmitriptan, rizatriptan may be expected to form an *N*-desmethyl derivative, which may be pharmacologically active. Except for sumatriptan (14% to 21% plasma protein binding[40]), we do not know the extent of plasma protein binding of the other drugs.

In conclusion, all current and prospective antimigraine drugs investigated contract the human coronary artery in vitro. Apart from avitriptan, therapeutic plasma concentrations of the drugs do not reach levels likely to cause myocardial ischemia in individuals with normal coronary circulation. However, like sumatriptan, all antimigraine compounds investigated, including the newer drugs, must remain contraindicated in patients with coronary artery disease. The sustained coronary artery contraction induced by ergotamine and dihydroergotamine is an important disadvantage compared with the sumatriptan-like drugs.

Acknowledgments

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