Coronary Side-Effect Potential of Current and Prospective Antimigraine Drugs

Antoinette MaasenVanDenBrink, MSc; Marije Reekers, MSc; Willem A. Bax, MD, PhD; Michel D. Ferrari, MD, PhD; Pramod R. Saxena, MD, PhD

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
Selected Abbreviations and Acronyms

Cmax = maximum plasma concentrations
EC50 = concentration eliciting 50% of its own Emax
Emax = maximum effect, maximum contraction
5-HT = 5-hydroxytryptamine
PGF2α = prostaglandin F2α

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, CaCl2 2.5, MgSO4 1.2, KH2PO4 1.2, NaHCO3 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% O2/5% CO2, 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 5-HT. In the first series of 9 experiments, a concentration-response curve was performed. After the relaxation was noted, the segments were then washed twice every 15 minutes, 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.

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, dihydroergotamine, methysergide, methylergometrine, sumatriptan, naratriptan, rizatriptan, avitriptan, and zolmitriptan) 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 Emax of the compounds tested was correlated with the relaxant response to substance P obtained in the individual coronary arteries (Pearson’s

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 EC50, 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 EC50 and Emax 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 Emax of the compounds tested was correlated with the relaxant response to substance P obtained in the individual coronary arteries (Pearson’s

Emax (Expressed as % of Effect Caused by 100 mmol/L K+) and EC50 (nmol/L) Values in Human Isolated Coronary Artery of 5-HT and Antimigraine Drugs, Together With Their Therapeutic Doses and Cmax in Patients

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC50, nmol/L</th>
<th>Emax, %K+</th>
<th>Dose, mg, Mode of Administration</th>
<th>Cmax, nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT</td>
<td>334 ± 99*</td>
<td>58.3 ± 7.9*</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>803 ± 197</td>
<td>14.0 ± 2.9</td>
<td>100 PO42</td>
<td>142–18342</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 SC42</td>
<td>244–26142</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>171 ± 36*</td>
<td>10.1 ± 2.1</td>
<td>2.5, 5 PO46</td>
<td>38, 7143</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>448 ± 88*</td>
<td>10.1 ± 2.7</td>
<td>10 PO44,46</td>
<td>74–9346</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>476 ± 87*</td>
<td>11.8 ± 2.5</td>
<td>2.5, 5 PO14,46</td>
<td>9, 1716</td>
</tr>
<tr>
<td>Avitriptan</td>
<td>89 ± 16*</td>
<td>7.7 ± 1.8</td>
<td>75, 150 PO42</td>
<td>628, 94821</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>17 ± 7*</td>
<td>20.5 ± 3.7</td>
<td>2 PO</td>
<td>0.03–0.6247,48</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>20 ± 10*</td>
<td>13.0 ± 2.5</td>
<td>0.75, 1 IM/SC43</td>
<td>3, 448</td>
</tr>
<tr>
<td>Methysergide†</td>
<td>243 ± 98*</td>
<td>7.8 ± 1.9</td>
<td>2 PO6</td>
<td>516</td>
</tr>
<tr>
<td>Methylergometrine†</td>
<td>46 ± 14*</td>
<td>13.4 ± 3.5</td>
<td>2 methysergide PO46</td>
<td>1416</td>
</tr>
</tbody>
</table>

*Significantly different from sumatriptan (P<0.05).
†Not used in acute migraine therapy.
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, 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$^+$. 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 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 of different drugs were not subjected to statistical analysis.

**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 and in vivo, 5-HT induced contraction of the isolated coronary artery. 5-HT was
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 methysergide26), 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 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 contract-
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potent as the parent compound in causing vasoconstriction. We do not know whether active metabolites are formed by 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.

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References


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