Stereoselective Interaction of Sulfinpyrazone with Racemic Warfarin and Its Separated Enantiomorphs in Man

ROBERT A. O'REILLY, M.D.

SUMMARY Although serious hemorrhage during therapeutic coadministration of sulfinpyrazone and racemic warfarin occurs, no prospective studies have been done. In this study, single oral doses of racemic warfarin, 1.5 mg/kg, were administered to six normal subjects with and without oral sulfinpyrazone, 400 mg daily. Both the hypoprothrombinemia (p < 0.001) and the plasma warfarin concentrations (p < 0.05) were significantly augmented. To determine if this interaction was stereoselective, the experiments were repeated in the same subjects with R- and S-warfarin enantiomers. S-warfarin with sulfinpyrazone caused a highly significant augmentation of both the hypoprothrombinemia (p < 0.001) and the plasma warfarin concentrations (p < 0.001). R-warfarin with sulfinpyrazone did not significantly change the hypoprothrombinemia but significantly (p < 0.05) reduced warfarin concentrations. Thus, sulfinpyrazone augmented the hypoprothrombinemia of racemic warfarin stereoselectively by reduced metabolic clearance of S-warfarin. Sulfinpyrazone and racemic warfarin are most dangerous when either drug is added to a stabilized regimen of the other drug.

SULFINPYRAZONE-INDUCED augmentation of the anticoagulant effect of racemic sodium warfarin was first observed in a patient in 1978.1 Since then, three other patients have been reported in whom the addition of sulfinpyrazone to their long-term regimen of racemic warfarin markedly potentiated the hypoprothrombinemia within 7–10 days.2, 3 Furthermore, seven patients on long-term therapy with sulfinpyrazone who each received only a single 10–15-mg dose of racemic warfarin also had an exaggerated anticoagulant effect, including severe gastrointestinal bleeding in one.4 The mechanism of the interaction was said to be displacement of albumin-bound warfarin by the sulfinpyrazone,1, 3 but no studies on the plasma concentrations of warfarin or displacement studies with specimens of patient blood were performed.4 To verify the interaction prospectively and to study its mechanism, the effect of sulfinpyrazone on the hypoprothrombinemia and plasma levels of racemic warfarin was studied in six normal subjects. Because this study showed marked potentiation of the anticoagulant effect of the racemate, the experiments were repeated in the same subjects with the separated enantiomorphs of racemic warfarin to determine if the interaction was stereoselective. The results of these experiments suggest a stereoselective mechanism for the interaction of sulfinpyrazone with racemic warfarin.

Methods

Subjects

Six men, 21–30 years old, were studied. All were paid volunteers who were carefully informed of the nature of the experiments and had signed written consents in accordance with all conditions required by federal regulation and the institutional review board. All were in excellent health and had not taken any other drug during the preceding 2 months. Each subject served as his own control, and the order of the experiments with warfarin alone and with warfarin combined with sulfinpyrazone in the crossover studies was assigned randomly.

Racemic Warfarin

A single dose of racemic sodium warfarin, 1.5 mg/kg body weight, was administered in tablet form by mouth, preceded randomly with or without sulfinpyrazone, to the six subjects. The dose was swallowed whole with a glassful of water during the postabsorptive state, and no food was ingested for the next 2 hours. Samples of venous blood were obtained for measurement of the plasma concentrations of warfarin and the one-stage prothrombin times just before the administration of the dose of warfarin and daily thereafter for the duration of the hypoprothrombinemic effect, usually about 10 days. The blood samples were mixed in glass tubes in a proportion of 9:1 with a combination of three parts 0.1 M sodium citrate and two parts 0.1 M citric acid and centrifuged at 2500 rpm for 30 minutes at 4°C. The plasma was removed and stored at −20°C.

After a 4-week rest period, sulfinpyrazone was administered twice a day before breakfast and after dinner as two tablets of 100 mg of drug each, which is the usual daily therapeutic dose of 400 mg. On day 4 of the sulfinpyrazone regimen, a single oral dose of racemic sodium warfarin, 1.5 mg/kg, was administered to each subject and blood samples were obtained daily throughout the period of hypoprothrombinemia, after which sulfinpyrazone was discontinued.

Warfarin Enantiomorphs

The enantiomorphs of racemic warfarin were separated by means of the method of West et al.5 The optical rotation of S-warfarin was −149°, which indicated essentially 100% optical purity, and that of R-
warfarin was +130°, which indicated 93% optical purity. The powdered enantiomorphs were placed in gelatin capsules. One month after the experiments with one enantiomorph of warfarin, the subjects received in random crossover experiments the other enantiomorph of warfarin, both with and without sulfinpyrazone. Thus, each subject participated in six separate experiments, two with the racemate and four with the enantiomorphs. Between experiments, there was a rest period of at least 4 weeks. Dosages of R-warfarin, 1.5 mg/kg, and the more potent S-warfarin, 0.75 mg/kg, were selected to yield comparable hypoprothrombinemic responses. The experimental procedure was exactly the same as for racemic warfarin.

One-stage Prothrombin Activity
The one-stage prothrombin activity was determined by means of the method of Quick. The total hypoprothrombinemic effect for each experiment for the control period of warfarin alone and the experimental period of warfarin plus sulfinpyrazone was ascertained by measuring the total area under the curve for the one-stage prothrombin time in seconds on a semilogarithmic scale (AUCp) and was expressed in arbitrary units.

Warfarin Measurement
The frozen plasma samples were thawed and a 0.5-ml aliquot was placed in a 20-ml scintillation vial and acidified with 0.5 ml 3N HCl and 1.0 ml water. The warfarin content was extracted into 8.0 ml of ethylene dichloride (Burlick and Jackson). The vials were shaken on a wrist-action shaker (Burrell Corp.) for 30 minutes. The recovery of warfarin was determined by split samples of normal plasma spiked with 0.5–10.0 μg/ml of 14C-labeled warfarin acid, and the counts after direct dilution and after the extraction procedure were compared. The amount recovered was 94% of 0.5 μg/ml warfarin, 92% of 1.0–2.0 μg/ml, and 91% of 3–10 μg/ml. The contents of the vials were centrifuged for 10 minutes at 5000 rpm at 10°C in nylon tubes. A 6.0-ml aliquot of the ethylene dichloride layer was evaporated to dryness by vacuum, dissolved in 500 μl degassed mobile phase, passed through a 5-μm Millipore filter in a Swinnex holder (Gelman Instruments), of which 100 μl was injected into a high-pressure liquid chromatographic (HPLC) apparatus.

The HPLC apparatus was Varian model 5020 pump (Varian Associates) with a sample-injection valve (Valco Instruments) and a radial compression module-100 (Waters Associates) containing a C18, 8-mm internal diameter cartridge. The mobile phase consisted of 2% glacial acetic acid in water:methanol (35:65, v/v), which was run at a flow rate of 2.0 ml/min. The ultraviolet detector was a Schoeffel Model 770 (Schoeffel Instrument) set at 315 nm and 0.04 absorbance units, full-scale sensitivity. The integrator of the HPLC peaks was an Autolab-System I (Spectra Physics).

The warfarin content of each plasma sample with and without sulfinpyrazone was quantitated in triplicate using an external standard. The appropriate external standards for racemic, S- and R-warfarin were 10.0 μg/ml, 5.0 μg/ml, and 1.0 μg/ml, respectively, added to a plasma blank and carried through the extraction procedure with the test samples. The warfarin content was corrected for the citrate anticoagulant added and the percent recovery of the external standard.

Unchanged warfarin had an HPLC retention time of 7.2–8.0 minutes. The more polar metabolic products of warfarin (6- and 7-hydroxywarfarin and the warfarin alcohols) eluted at 3.0–5.5 minutes. The even more polar-unchanged sulfinpyrazone and sulfinpyrazone metabolites plus degradation products were eluted well before the metabolic products of warfarin and could not be detected at 315 nm. The small amounts of warfarin in the 216-hour plasma specimens, 0.05–0.50 μg/ml, were easily quantitated.

Statistical Analysis
Comparative data are expressed as mean ± SEM. As each subject served as his own control, the significance of differences was assessed by the t test for paired observations (one-tailed). Significance of data was determined at the level of p < 0.05.

Results
One-stage Prothrombin Activity
All of the subjects had detectable reduction of the one-stage prothrombin activity 24 hours after ingestion of all three forms of warfarin, both with and without sulfinpyrazone (table 1). With racemic warfarin, the mean of the lowest one-stage prothrombin activity occurred at 60 hours with the anticoagulant alone and at 72 hours with anticoagulant plus sulfinpyrazone. The mean time of return of the one-stage prothrombin to 70% of normal activity was 144 hours with racemic warfarin alone and was 228 hours with anticoagulant plus sulfinpyrazone. The means of the hypoprothrombinemia for racemic warfarin alone and with sulfinpyrazone during the first 24 hours were not significantly different, but the means during the sulfinpyrazone regimen were more depressed at 48–72 and 240 hours (p < 0.05) and 96–168 and 216 hours (p < 0.01) and 192 hours (p < 0.001) than the means during racemic warfarin alone.

With S-warfarin, the mean of the lowest one-stage prothrombin activity occurred at 48 hours with the anticoagulant alone and at 84 hours with anticoagulant plus sulfinpyrazone. The mean time of return of the one-stage prothrombin to 70% of normal activity was 108 hours with S-warfarin alone and was greater than 228 hours with anticoagulant plus sulfinpyrazone. The means of the hypoprothrombinemia for S-warfarin alone and with sulfinpyrazone during the first 48 hours were not significantly different, but the means during the sulfinpyrazone regimen were more depressed at 216–240 hours (p < 0.05) and 72–120 hours (p < 0.01) and 144–192 hours (p < 0.001) than the means during S-warfarin alone.

With R-warfarin, the mean of the lowest one-stage prothrombin activity occurred at 48 hours both with...
TABLE 1. One-stage Prothrombin Activity after Single Doses of Racemic Warfarin and Its Separated Enantiomorphs, S-warfarin and R-warfarin, With and Without Daily Sulfinpyrazone in Six Normal Subjects*

<table>
<thead>
<tr>
<th></th>
<th>One-stage prothrombin activity, hours after warfarin dose</th>
<th>AUC&lt;sub&gt;p&lt;/sub&gt; (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0  24  48  72  96  120  144  168  192  216  240</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(% of normal activity)</td>
<td></td>
</tr>
<tr>
<td>Racemic warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>100 ± 0 61 ± 5 31 ± 2† 42 ± 8‡ 70 ± 12‡ 95 ± 11 § 77 ± 17 §</td>
<td></td>
</tr>
<tr>
<td>With SPZ</td>
<td>100 ± 0 54 ± 4 25 ± 2‡ 22 ± 3‡ 25 ± 3‡ 31 ± 3‡ 38 ± 5‡</td>
<td></td>
</tr>
<tr>
<td>S-warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>100 ± 0 51 ± 11 33 ± 4 64 ± 12‡ 75 ± 14‡ 82 ± 12§ 92 ± 5 § 79 ± 0 §</td>
<td></td>
</tr>
<tr>
<td>With SPZ</td>
<td>100 ± 0 53 ± 2 27 ± 2 25 ± 2‡ 25 ± 4‡ 32 ± 5‡</td>
<td></td>
</tr>
<tr>
<td>R-warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>100 ± 0 58 ± 4 36 ± 3 41 ± 3 55 ± 5 73 ± 6</td>
<td></td>
</tr>
<tr>
<td>With SPZ</td>
<td>100 ± 0 53 ± 2 34 ± 2 39 ± 3 54 ± 5 69 ± 7</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*Racemic warfarin, 1.5 mg/kg orally; S-warfarin, 0.75 mg/kg orally; R-warfarin, 1.5 mg/kg orally; SPZ, 400 mg daily beginning 3 days before the warfarin dose and continuing for the duration of the hypoprothrombinemia.

†<i>p</i> < 0.05.
‡<i>p</i> < 0.01.
§<i>p</i> < 0.001.

Abbreviations: AUC<sub>p</sub> = total area under one-stage prothrombin time on logarithmic scale, expressed in arbitrary units; SPZ = sulfinpyrazone.

the anticoagulant alone and with anticoagulant plus sulfinpyrazone. The mean time of return of the one-stage prothrombin to 70% of normal activity was 108 hours with and 132 hours without sulfinpyrazone. The means of the hypoprothrombinemia for R-warfarin alone and with sulfinpyrazone from 0–240 hours were not significantly different at any of the times tested (<i>p</i> > 0.20).

The AUC<sub>p</sub> increased markedly from control values for racemic warfarin alone in all six subjects after sulfinpyrazone was administered concurrently with racemic warfarin. The increase of the mean AUC<sub>p</sub> was

Figure 1. Means (± SEM) of plasma concentrations of warfarin and one-stage prothrombin times after single oral doses of racemic sodium warfarin, S-warfarin and R-warfarin with and without daily doses of sulfinpyrazone. Sulfinpyrazone, 400 mg daily by mouth, was administered for 3 days before the warfarin dose and for the duration of the hypoprothrombinemia. The lines for the half-life (T½) of warfarin concentrations were computed by the least-squares method. On the lower graph, the ordinate on the left expresses the one-stage prothrombin time and on the right expresses it in the percentage of normal activity. With racemic warfarin, sulfinpyrazone prolonged the half-life of warfarin and augmented the hypoprothrombinemia; with S-warfarin it markedly prolonged the T½ of warfarin and markedly augmented the hypoprothrombinemia; with R-warfarin it shortened the half-life of warfarin and had little effect on the hypoprothrombinemia.
199% of the control value, from 77 ± 17 to 153 ± 19 units, a highly significant difference (p < 0.001). For S-warfarin alone, the mean AUC_p increased from control values in all six subjects after sulfinpyrazone was administered concurrently with S-warfarin. The increase of the mean AUC_p was 264% of the control value, from 52 ± 15 to 137 ± 15 units, a highly significant difference (p < 0.001). For R-warfarin alone the AUC_p increased from control values in four subjects and decreased in two subjects after sulfinpyrazone was administered concurrently with R-warfarin (table 1, fig. 1). The increase of the mean AUC_p was 114% of the control value, from 49 ± 7 to 56 ± 6, an insignificant difference (p > 0.20).

Plasma Concentrations of Warfarin

With racemic warfarin, the mean values of the plasma concentrations of warfarin for the anticoagulant alone and with sulfinpyrazone during the first 48 hours were not significantly different, but the means during the sulfinpyrazone regimen were higher at 72–96 hours (p < 0.05) and at 120–216 hours (p < 0.01) than the means for racemic warfarin alone (table 2). The AUC_w for racemic warfarin during the sulfinpyrazone regimen increased in all six subjects and the mean AUC_w was significantly higher (p < 0.05) than the mean for the anticoagulant alone.

With S-warfarin, the means of the plasma concentrations of warfarin for the anticoagulant with sulfinpyrazone were significantly higher at 24 hours (p < 0.05), at 48 hours (p < 0.01), and at 72–216 hours (p < 0.001). The AUC_w for S-warfarin during the sulfinpyrazone regimen was increased in all six subjects and the mean AUC_w was higher to a highly significant degree (p < 0.001) than the mean AUC_w for the anticoagulant alone.

With R-warfarin, the means of the plasma concentrations of warfarin for the anticoagulant with sulfinpyrazone were significantly lower at 24 hours (p < 0.05) and at 48–216 hours (p < 0.01). The AUC_w for R-warfarin during the sulfinpyrazone regimen was decreased in all six subjects and the mean AUC_w was significantly lower (p < 0.01) than the mean AUC_w for anticoagulant alone.

Kinetic Analysis of Plasma Concentrations of Warfarin

With racemic warfarin, the plasma half-life of the warfarin concentrations (t½) increased in all six subjects, and the mean t½ was significantly longer (p < 0.05) during the sulfinpyrazone regimen than during the anticoagulant alone (table 3). The means for the apparent volume of distribution (Vd) were not significantly different (p > 0.20) for racemic warfarin alone and during the sulfinpyrazone regimen. The mean AUC_w for racemic warfarin was significantly larger (p < 0.05) during the sulfinpyrazone regimen. The mean plasma clearance for racemic warfarin decreased significantly (p < 0.05) during the sulfinpyrazone regimen.

With S-warfarin, the t½ increased markedly in all six subjects, and the mean t½ increased significantly (p < 0.001) during the sulfinpyrazone regimen compared with the mean t½ for the anticoagulant alone. The means for Vd were not significantly different for S-warfarin alone and during the sulfinpyrazone regimen (p > 0.20). The mean AUC_w for S-warfarin was

---

**Table 2. Plasma Concentrations of Warfarin after Single Doses of Racemic Warfarin and Its Separated Enantiomorphs, S-warfarin and R-warfarin, With and Without Daily Sulfinpyrazone in Six Normal Subjects**

<table>
<thead>
<tr>
<th>Warfarin concentrations in plasma, hours after warfarin dose</th>
<th>24 (µg/ml)</th>
<th>48 (µg/ml)</th>
<th>72 (µg/ml)</th>
<th>96 (µg/ml)</th>
<th>120 (µg/ml)</th>
<th>144 (µg/ml)</th>
<th>168 (µg/ml)</th>
<th>192 (µg/ml)</th>
<th>216 (µg/ml)</th>
<th>AUC_w (µg/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Racemic warfarin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>8.77 ± 0.50</td>
<td>5.86 ± 0.41</td>
<td>3.93 ± 0.35</td>
<td>2.64 ± 0.29</td>
<td>1.79 ± 0.23</td>
<td>1.21 ± 0.18</td>
<td>0.82 ± 0.14</td>
<td>0.56 ± 0.10</td>
<td>0.39 ± 0.08</td>
<td>7.01 ± 6.11</td>
</tr>
<tr>
<td>With SPZ</td>
<td>8.82 ± 0.42</td>
<td>6.29 ± 0.36</td>
<td>4.51 ± 0.33</td>
<td>3.24 ± 0.30</td>
<td>2.33 ± 0.26</td>
<td>1.69 ± 0.18</td>
<td>1.22 ± 0.15</td>
<td>0.89 ± 0.12</td>
<td>0.65 ± 0.56</td>
<td>7.70 ± 4.16</td>
</tr>
<tr>
<td><strong>S-warfarin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>3.92 ± 0.40</td>
<td>2.32 ± 0.37</td>
<td>1.40 ± 0.29</td>
<td>0.86 ± 0.22</td>
<td>0.54 ± 0.16</td>
<td>0.34 ± 0.11</td>
<td>0.28 ± 0.07</td>
<td>0.14 ± 0.05</td>
<td>0.09 ± 0.03</td>
<td>2.61 ± 4.16</td>
</tr>
<tr>
<td>With SPZ</td>
<td>5.53 ± 0.40</td>
<td>3.98 ± 0.25</td>
<td>2.87 ± 0.25</td>
<td>2.08 ± 0.20</td>
<td>1.50 ± 0.17</td>
<td>1.09 ± 0.14</td>
<td>0.79 ± 0.09</td>
<td>0.58 ± 0.42</td>
<td>0.42 ± 0.50</td>
<td>5.03 ± 4.41</td>
</tr>
<tr>
<td><strong>R-warfarin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>9.25 ± 0.47</td>
<td>6.41 ± 0.31</td>
<td>4.44 ± 0.22</td>
<td>3.08 ± 0.18</td>
<td>2.14 ± 0.12</td>
<td>1.50 ± 0.11</td>
<td>1.04 ± 0.10</td>
<td>0.73 ± 0.08</td>
<td>0.51 ± 0.06</td>
<td>7.36 ± 3.22</td>
</tr>
<tr>
<td>With SPZ</td>
<td>8.16 ± 0.51</td>
<td>5.24 ± 0.38</td>
<td>3.38 ± 0.24</td>
<td>2.18 ± 0.18</td>
<td>1.41 ± 0.14</td>
<td>0.92 ± 0.10</td>
<td>0.60 ± 0.07</td>
<td>0.39 ± 0.05</td>
<td>0.26 ± 0.05</td>
<td>5.74 ± 0.55</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*Racemic warfarin, 1.5 mg/kg orally; S-warfarin, 0.75 mg/kg orally; R-warfarin, 1.5 mg/kg orally; SPZ, 400 mg daily beginning 3 days before the warfarin dose and continuing for the duration of the hypoprothrombinemia.

_tp < 0.05.

_tp < 0.01.

_SPZ < 0.001.

Abbreviations: AUC_w = total area under curves for plasma concentrations of warfarin; SPZ = sulfinpyrazone.
<table>
<thead>
<tr>
<th>Drug</th>
<th>1/2 (hour)</th>
<th>β (hour⁻¹)</th>
<th>Vd (l)</th>
<th>AUC∞ (μg/ml·hr)</th>
<th>Cl (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Racemic warfarin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>41.8 ± 2.9</td>
<td>0.0170</td>
<td>8.8</td>
<td>701</td>
<td>2.51</td>
</tr>
<tr>
<td>With SPZ</td>
<td>50.4 ± 3.5</td>
<td>0.0141</td>
<td>9.4</td>
<td>770</td>
<td>2.26</td>
</tr>
<tr>
<td>S-warfarin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>31.9 ± 3.6</td>
<td>0.0234</td>
<td>9.0</td>
<td>261</td>
<td>3.76</td>
</tr>
<tr>
<td>With SPZ</td>
<td>51.3 ± 3.0</td>
<td>0.0137</td>
<td>7.8</td>
<td>503</td>
<td>1.83</td>
</tr>
<tr>
<td>R-warfarin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>45.3 ± 2.5</td>
<td>0.0153</td>
<td>8.9</td>
<td>736</td>
<td>2.38</td>
</tr>
<tr>
<td>With SPZ</td>
<td>37.8 ± 2.1</td>
<td>0.0187</td>
<td>9.4</td>
<td>574</td>
<td>3.09</td>
</tr>
</tbody>
</table>

* Racemic warfarin, 1.5 mg/kg orally; S-warfarin, 0.75 mg/kg orally; R-warfarin, 1.5 mg/kg, orally; SPZ, 400 mg daily beginning 3 days before the warfarin dose and continuing for the duration of the hypoprothrombinemia.

† P < 0.05.
† P < 0.01.
§ P < 0.001.

**Abbreviations:** 1/2 = half-life of warfarin concentrations calculated by least-squares methods; β = slope of the terminal phase of plasma concentrations of warfarin; Vd = apparent volume of distribution, calculated from D/Cp₀, where D is dose of warfarin and Cp₀ is plasma concentrations of warfarin at time 0, calculated by extension of β; AUC∞ = total area under curve for plasma concentrations of warfarin; Cl = warfarin clearance, calculated from (Vd · β + D/AUC∞)/2, the average of two methods for calculating clearance.

By guest on July 26, 2017 http://circ.ahajournals.org/ Downloaded from

significantly larger (p < 0.001) during the sulfinpyrazone regimen. The mean plasma clearance for S-warfarin decreased significantly (p < 0.001) during the sulfinpyrazone regimen.

With R-warfarin, the mean plasma 1/2 during the sulfinpyrazone regimen was significantly shorter (p < 0.05) than the mean for the anticoagulant alone. The means for Vd were not significantly different for R-warfarin alone and during the sulfinpyrazone regimen (p > 0.20). The mean AUC∞ for R-warfarin was significantly smaller (p < 0.01) during the sulfinpyrazone regimen. The mean plasma clearance for R-warfarin increased significantly (p < 0.05) during sulfinpyrazone.

**Discussion**

The results with racemic warfarin with and without sulfinpyrazone, wherein the augmentation of the hypoprothrombinemia was much greater than that of the plasma concentrations of warfarin, may be explained by the data obtained with the separated enantiomorphs. The highly significant increase in the plasma concentrations of S-warfarin (p < 0.01) was partially offset by the significant decrease in the plasma concentrations of R-warfarin (p < 0.05) during the sulfinpyrazone regimen. In a study on the interaction of trimethoprim-sulfamethoxazole and racemic warfarin, the changes in the plasma concentrations of S-warfarin and R-warfarin completely offset each other, which caused no significant change in the plasma concentrations of warfarin after administration of the racemate and resulted in a concealed pharmacokinetic basis of the interaction. In a study on the interaction of phenylbutazone and racemic warfarin in man, the plasma concentrations of the racemate decreased because the increase in the plasma concentrations of S-warfarin was more than offset by the marked decrease in the plasma concentrations of R-warfarin during the phenylbutazone regimen.

We propose the following mechanism for the interaction of sulfinpyrazone with racemic warfarin. S-warfarin is metabolically transformed mainly by oxidation through ring hydroxylation of the coumarin nucleus to 7-hydroxy-S-warfarin, which is eliminated by the liver primarily into the bile and eventually into the stool. R-warfarin is metabolically transformed mainly by reduction of the ketone group of the acetonyl side chain to secondary alcohols, which are excreted primarily by the kidney into the urine. The activity of the enzymes that control the ring oxidation of S-warfarin could be inhibited by sulfinpyrazone. This inhibition of the metabolic transformation of S-warfarin would impair its total body clearance and lead to higher plasma concentrations and a longer 1/2 in plasma for unchanged S-warfarin. The activity of the enzymes that control the reduction of the side chain of R-warfarin may be increased by enzymatic
induction by sulfinpyrazone, as reported for phenylbutazone. This would increase the total body clearance of R-warfarin and lead to the lower plasma concentrations and a shorter t½ in plasma for unchanged R-warfarin.

The altered metabolic clearances of S-warfarin and R-warfarin also could result from mechanisms other than direct hepatic effects on the metabolic transformation of the warfarin enantiomorphs by sulfinpyrazone. Altered renal clearance, reported for the effect of quinidine on the serum concentrations of digoxin, is unlikely because unchanged warfarin is so highly protein-bound that its urinary excretion is negligible. Displacement of albumin-bound warfarin with altered concentrations of the warfarin enantiomorphs at the hepatic receptor sites for the synthesis of the vitamin K-dependent clotting factors is under investigation and has been demonstrated in vitro for the interaction of sulfinpyrazone and the coumarin anticoagulant phenprocoumon.

A paradox of the present study is the highly significant increase of both the plasma concentrations of drug and the hypoprothrombinemia with S-warfarin during the sulfinpyrazone regimen (p < 0.001), while with R-warfarin plus the sulfinpyrazone regimen, the significant decrease (p < 0.05) in the plasma concentrations of anticoagulant drug was associated with a slight increase (14%) in the one-stage prothrombin time. This discrepancy between the plasma concentrations of R-warfarin and its hypoprothrombinemic response during a drug interaction was also observed with another pyrazole derivative, phenylbutazone, in which a marked decrease in the plasma concentrations of R-warfarin was accompanied by no significant change in the hypoprothrombinemic response (O'Reilly RA: unpublished observations). However, neither sulfinpyrazone nor phenylbutazone administered alone have any effect on the prothrombin time.

Sulfinpyrazone augmented the hypoprothrombinemia of racemic warfarin stereoselectively by reducing the metabolic clearance of S-warfarin. The lack of hypoprothrombinemic interaction with R-warfarin suggests that the danger of hemorrhage may be lessened in long-term therapy compared with racemic warfarin. Patients simultaneously begun on racemic warfarin and sulfinpyrazone, like patients with prosthetic heart valves, do not have a significant increase in hemorrhagic episodes because monitoring of the prothrombin time leads to a lower daily dose of warfarin than if the warfarin were administered alone. However, when either drug is added to a stabilized regimen of the other drug, an exaggerated anticoagulant effect will occur and serious bleeding may ensue. Sulfinpyrazone may be more dangerous than other drugs that prolong the prothrombin time of racemic warfarin because not only does it inhibit platelet func-

tion, but, unlike aspirin, it also has hemodynamic effects.

Acknowledgment
I am indebted to Dr. Collin Schroeder of the Wisconsin Alumni Research Foundation of Madison, Wisconsin for supplying the enantiomers of warfarin and to Dr. William Trager of the University of Washington School of Pharmacy of Seattle, Washington for measuring their optical rotation, and to Catherine Motley, Susan Nutter, and Marjorie Kline for their assistance.

References
Stereoselective interaction of sulfinpyrazone with racemic warfarin and its separated enantiomorphs in man.

R A O'Reilly

*Circulation*. 1982;65:202-207
doi: 10.1161/01.CIR.65.1.202

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/65/1/202

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org/subscriptions/