A Double-Blind Clinical Trial to Determine if an Interaction Exists Between Diclofenac Sodium and the Oral Anticoagulant Acenocoumarol (Nicoumalone)

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A double-blind crossover trial between diclofenac sodium and placebo was carried out in 32 hospitalized patients who were thought to be stabilized on concurrent anticoagulant therapy with acenocoumarol. The object of the trial was to investigate any possible interaction between diclofenac and anticoagulant by monitoring prothrombin times daily through the four week period. No statistically significant difference between placebo and diclofenac could be shown and some problems of accurately monitoring prothrombin times are discussed.

Introduction
It is well known that careful monitoring of prothrombin time is essential whenever a drug is added to or withdrawn from the regimen of any patient receiving anticoagulants. The list of drugs which interact with anticoagulants is impressive (O'Reilly & Levi 1970, Breckenridge et al 1971, Van Dam & Gribau-Overkamp 1967, Hoffbrand & Kinmonth 1967, Koch-Weser & Sellers 1971) and it is, therefore, of great importance to investigate any new compound with regard to possible anticoagulant interaction.

Diclofenac sodium (Voltaren®—Ciba-Geigy) is a new anti-inflammatory agent with analgesic properties, which seems particularly suitable for use in rheumatoid conditions and this trial was carried out to compare the anticoagulant effect of acenocoumarol (*Sintrom®—Ciba-Geigy) in patients treated with either diclofenac sodium or placebo.

* Sintrom®. Geigy, UK

Patients and Methods
Thirty-two hospitalized patients (19 males; 13 females) who were thought to be adequately stabilized on oral anticoagulant therapy and who required concomitant analgesic and/or anti-inflammatory medication with acenocoumarol were entered into the trial. All patients had previously given their informed consent and the median age of the trial population was 61.4 years. The patients of the two treatment sequences were homogeneous for sex and median age. The patients were treated throughout the 4-week trial period with a therapeutically optimal dose of acenocoumarol.

The indication for anticoagulant therapy was thrombophlebitis in the deep veins (with or without lung embolism) in 12 patients (37.5%), lung embolism alone in five patients (15.6%), myocardial infarction in eight patients (25.0%), and in the other seven patients (21.9%) anticoagulant therapy was given for various indications such as angina.
pectoris and cardioversion. Concomitant disease was present in 28 of 32 patients.

A pre-treatment general laboratory investigation was conducted to ensure that patients with severe liver or kidney diseases were excluded from the trial. Several pre-treatment laboratory abnormalities of blood, serum and urine were present of which most were undoubtedly due to the disease for which the anticoagulant therapy was given and/or to the concomitant disease(s). However, as none of those abnormalities were considered clinically to be a reason for excluding the patients from the trials, none of the patients were excluded from the statistical analysis. No patient suffered from severe liver or kidney disease.

During weeks 1 and 4 of the trial baseline measurements were obtained, while in weeks 2 and 3 patients were randomly assigned to receive, in addition to acenocoumarol, one week's treatment with, first, diclofenac sodium (25 mg q.i.d.) and secondly, placebo or the two medications in the reverse order. Throughout the trial the prothrombin time (Quick's Test with Fibrosystem and Brain-thrombokinase) was performed daily and recorded along with the daily dose of acenocoumarol which was adjusted in accordance with the prothrombin time of the previous day.

Results

In three patients the prothrombin value was not recorded daily and so, for the statistical analysis, only 29 patients were included. Of these, 15 received diclofenac sodium first and placebo second and 14 received placebo in week 2 and diclofenac sodium in week 3.

The mean values of the acenocoumarol dose and the mean prothrombin value for each week of the trial are shown in Table 1. As can be seen from this table, the correlation between the mean anticoagulant dose and the mean prothrombin value was least in week 1. Thus, in the first treatment sequence a mean daily dose of 3·1 mg acenocoumarol resulted in a mean prothrombin value of 27·2% while a higher mean daily acenocoumarol dose of 4·0 mg in the second treatment sequence did not, as expected, result in a lower prothrombin time than that of the first treatment sequence, but in a higher value. Thus it is likely that during the first week of the trial the acenocoumarol dose was still being adjusted. This impression is confirmed by the finding that the frequency of prothrombin values outside the therapeutic range (i.e. < 15% or > 25%) was significantly higher in week 1 than in any of the succeeding weeks (see Table 2).

However, during weeks 2 and 3 of the trial when the crossover took place, the frequency of prothrombin values outside the therapeutic range was statistically the same for diclofenac sodium and placebo (see Table 2). Furthermore, the amount of acenocoumarol given to bring the prothrombin value within the therapeutic range was

| Table 1 |
| Mean values of acenocoumarol (mg) and prothrombin value (%) |

<table>
<thead>
<tr>
<th>Treatment sequence</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>P</td>
<td>A</td>
<td>P</td>
</tr>
<tr>
<td>Diclofenac-Na</td>
<td>3·1</td>
<td>27·2</td>
<td>2·8</td>
<td>26·0</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>4·0</td>
<td>30·6</td>
<td>3·3</td>
<td>25·5</td>
</tr>
<tr>
<td>Diclofenac-Na</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A = acenocoumarol dose (mg)
P = prothrombin value (%)
### Table 2

**Proportion of prothrombin values out of treatment range**

<table>
<thead>
<tr>
<th>Treatment sequence</th>
<th>Week 1 (6 days)*</th>
<th>Week 2 (7 days)*</th>
<th>Week 3 (7 days)*</th>
<th>Week 4 (6 days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac-Na</td>
<td>54/90</td>
<td>51/105</td>
<td>48/105</td>
<td>40/90</td>
</tr>
<tr>
<td>Placebo (n = 15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>64/84</td>
<td>45/98</td>
<td>34/98</td>
<td>44/84</td>
</tr>
<tr>
<td>Diclofenac-Na</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 14)</td>
<td>118/174</td>
<td>96/203</td>
<td>82/203</td>
<td>84/174</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = No of patients

*Refers to number of days/week for which paired values for acenocoumarol dose and prothrombin value were obtained.

The data obtained during weeks 2 and 3 were also examined by determining the correlation coefficient (r) for each patient for each week between the dose of acenocoumarol and its anticoagulant effect as measured by the prothrombin test for each patient for each week. As can be seen from Figure 1, the greater the spread between the points obtained when one plots for each week the daily dose of acenocoumarol against the prothrombin value obtained in the succeeding day, the lower the correlation and thus the lower the r value.

The majority of the resulting correlation coefficients are negative because, as is to be expected, the higher the dose of anticoagulant the lower the resulting prothrombin value. The mean correlation coefficients obtained were:

- **Week 2**
  
  - Diclofenac sodium: $r = -0.385$
  - Placebo: $r = -0.341$

- **Week 3**
  
  - Diclofenac sodium: $r = -0.277$
  - Placebo: $r = -0.320$

An analysis of variance was conducted with the correlation coefficients and did not reveal any statistical significance between either the two treatments or the two weeks. In other words, no significant treatment or order effect was present.

None of the patients required vitamin K and no unwanted effects were reported.

## Discussion

Patients were entered into the trial who were believed to be stabilized on oral anticoagulant therapy. However, the findings that the correlation between the mean anticoagulant dose and the mean prothrombin value was least in week 1 and that the proportion of prothrombin values outside the therapeutic range was also highest in the first week would appear to indicate that the patients were not fully stabilized on anticoagulants. The reason for this may be the fact that before commencement of the trial the prothrombin time of the patients was controlled once every 2–3 days and, as would be expected, with daily prothrombin time determinations, anticoagulant requirements of the patient can be better estimated.

The failure to demonstrate a statistically significant difference between diclofenac sodium and placebo in the correlation between the mean acenocoumarol dose and the mean prothrombin value, the proportion...
of prothrombin values out of the therapeutic range and in the correlation coefficients between these two variables, would indicate that in this trial no clinically significant interaction between 100 mg daily of diclofenac sodium and acenocoumarol occurred. These results are in agreement with the findings of Breddin (1975) who examined the effect on prothrombin time of giving 75 mg daily of diclofenac sodium for two weeks to 13 patients who were established on long-term treatment with phenprocoumon. No clinically important interaction between phenprocoumon and diclofenac sodium was noted in this trial.

**Conclusion**

The results of this trial indicate that the concomitant administration of 100 mg daily of diclofenac sodium is not likely to affect the anticoagulant effect of acenocoumarol and almost certainly not to a clinically significant extent.
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