Reduction in the Intensity of Abortive Migraine Drug Use During Coumarin Therapy

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Objective.—To investigate the impact of coumarin therapy on migraine attack frequency.

Background.—Sporadic case reports and clinical studies have described beneficial effects of coumarin therapy on migraine severity.

Design and Methods.—A retrospective follow-up study based on a prescription database covering a population of 450000 was conducted. All patients using an abortive migraine drug (ergotamine or sumatriptan) and subsequently treated with either coumarin (index group) or low-dose acetylsalicylic acid (control group) were analyzed. The impact of coumarin and low-dose acetylsalicylic acid on the frequency of migraine attacks was assessed by measuring the intensity of ergotamine and sumatriptan use, in defined daily doses per month per patient, before and during coumarin or acetylsalicylic acid treatment. In addition, a "therapeutic intensity reduction" was determined for each patient.

Results.—The study population consisted of 92 patients; 35% had been prescribed coumarin and 65% had been prescribed low-dose acetylsalicylic acid after the initiation of ergotamine or sumatriptan. Two thirds of the study population was treated with ergotamine. Overall, ergotamine and sumatriptan use for the coumarin cohort decreased from 6.4 defined daily doses per month prior to coumarin treatment to 3.0 defined daily doses during coumarin treatment, compared with a reduction from 5.2 defined daily doses per month to 4.4 defined daily doses per month for the low-dose acetylsalicylic acid cohort ($P>.05$). The therapeutic intensity of ergotamine and sumatriptan use was significantly decreased by 40% for the coumarin cohort, compared with 4.7% for the low-dose acetylsalicylic acid cohort ($P=.004$).

Conclusions.—We observed that coumarin treatment was clearly associated with a reduction in the therapeutic intensity of abortive migraine drug use in comparison with low-dose aspirin treatment. This suggests that, overall, the coumarin cohort had experienced a substantial reduction in the frequency of migraine attacks during anticoagulation treatment. Our findings, as well as those of others, justify a controlled clinical trial to further establish the effects of coumarin therapy on migraine severity and its possible role in the prophylactic management of patients suffering from migraine.

Key words: anticoagulation, impact, migraine, ergotamine, sumatriptan, consumption

Abbreviations: DDDs defined daily doses, OAC oral anticoagulation with coumarin derivatives, ASA acetylsalicylic acid

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A few case reports have described a complete resolution of migraine or a substantial reduction in frequency and intensity of migraine attacks in migraineurs with or without aura during treatment with oral anticoagulant drugs, such as warfarin or acenocoumarol.[1-4] In addition, a recent patient questionnaire study in 400 subjects treated with acenocoumarol for nonneurological indications revealed that oral anticoagulation produced improvement of headache in 63% of patients with migraine versus 38% of patients with nonmigrainous headache.[5] Although the

underlying mechanism associated with the possible improvement of migraine symptoms due to coumarin therapy has not been fully elucidated, there is evidence that during migraine attacks there is an increase in platelet aggregability and plasma coagulability. The association between prothrombotic processes and migraine has been linked to the risk of migraine-induced stroke.[6-8]

Suggestions have been made that warfarin or acenocoumarol when prescribed at low doses could be considered as a prophylactic treatment for patients with resistant forms of migraine.[2,5] However, controlled studies are lacking. This means that the possible reduction in migraine attack frequency and severity due to the use of oral anticoagulation therapy requires further confirmation.

The objective of this observational retrospective follow-up study was to evaluate the nature and strength of the association between oral anticoagulation therapy and severity of migraine by evaluating the therapeutic intensity of ergotamine and sumatriptan use before and during oral anticoagulation therapy.

METHODS

Study Setting.—The study used prescription data from the PHARMO-RLS database located at the University of Utrecht, The Netherlands, covering the period from 1985 to 1998. This database has been described elsewhere.[9] In brief, the system was designed in 1985 to provide relevant demographic and prescription data at an individual level for five medium-sized cities in The Netherlands from 1985 to 1989. Since 1990, it has been further updated, covering a total of six cities (n=300000), and from 1993 to 1998, eight cities (n=450000). Most patients in The Netherlands adhere to their registered pharmacy, and due to sophisticated pharmacy software currently available, the prescription medication information for each patient is virtually complete, thus allowing observation of patient medication use over time.

Each registered person is identified with an anonymous unique patient identification code. Retrievable information per prescribed medicine includes date of dispensing, drug, dosage regimen, quantity supplied (defined daily doses [DDDs]), and type of prescriber. Patient information per prescribed medicine includes gender and date of birth. The database does not provide information concerning the indications for use of the medicines, in this case the diagnosis of migraine versus cluster headache, or registration of nonprescription medicines (eg, over-the-counter [OTC] use of salicylates or paracetamol).

Study Population.—All patients who presented more than one prescription for an abortive migraine drug (either ergotamine or sumatriptan) as well as a prescription for acenocoumarol/fenprocoumon (OAC) or low-dose acetylsalicylic acid (ASA) for the first time from June 1, 1985 to December 31, 1998 were initially identified.

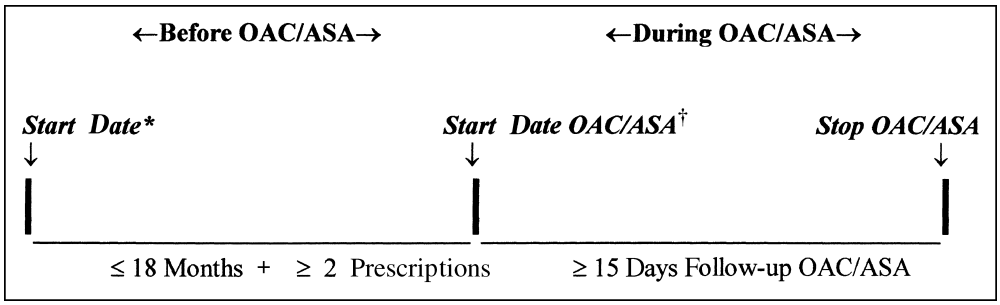
For each patient included in the study, the date of first prescription of either abortive migraine drug was termed the *start date*.

Patients were subsequently categorized into two cohorts: patients commencing oral anticoagulation therapy with OAC (index group) or patients commencing ASA (control group) following the start date of the abortive migraine drug. The first prescription for anticoagulation with OAC or ASA was termed *start date OAC/ASA* (Figure).

For eligibility, patients included in the two cohorts had to fulfill all of the following criteria:

1. The patients received anticoagulation therapy of at least 15 days' duration, defined as the time span between the first and last prescription of anticoagulation.
2. The patient did not use OAC and ASA simultaneously.
3. The patient did not use or start migraine prophylactic therapy (propranolol, metoprolol, pizotifen, clonidine, flunarizine, or methysergide) before or after the start date OAC/ASA.
4. The patient presented at least two prescriptions for either ergotamine or sumatriptan during 18 months preceding the start date of OAC/ASA.

Data Analysis.—For each identified patient, a few baseline characteristics were determined from the database including age (determined at start date OAC/ASA), gender, and duration of anticoagulant therapy.



Study design. *Start date corresponds to the date of the first prescription for specific abortive migraine drug use. †OAC/ASA corresponds to the date of the first prescription for either acenocoumarol/fenprocoumon or low-dose acetylsalicylic acid.

The outcome of interest in this study was the change in the frequency of migraine attacks before and during OAC/ASA use for each patient. To examine potential changes in the frequency of attacks, we measured the consumption of ergotamine and sumatriptan in terms of DDDs per month before and during OAC/ASA treatment. This measurement of drug utilization was termed the *therapeutic intensity* of abortive migraine drug use. Changes in drug consumption over time have been applied as a tool to assess changes in levels of disease severity.[10,11] One DDD of sumatriptan corresponds to one 100-mg tablet or one 6-mg subcutaneous injection; one DDD of ergotamine corresponds to 4-mg ergotamine or 2-mg ergotamine combined with cyclizine/caffeine by any route of administration. The therapeutic intensity for each patient was calculated by dividing the absolute number of DDDs dispensed per prescription by the number of days between the first and last prescription presented during an 18-month follow-up period preceding the start date of OAC/ASA and during the period of use of OAC/ASA.

To express the impact of OAC as well as ASA therapy on migraine analgesic consumption, we calculated a *therapeutic intensity reduction* for each patient. Therapeutic intensity reduction was defined as:

$$1 - \frac{\text{therapeutic intensity } \textit{during} \text{ OAC/ASA}}{\text{therapeutic intensity } \textit{before} \text{ OAC/ASA}}$$

The nonparametric Mann-Whitney *U* test was used to evaluate the results.

Microsoft Access, a relational database software package, was used for database management and internal quality and validation procedures. The Statistical Package for the Social Sciences (SPSS) for Windows was used for data analysis.

RESULTS

Among the study pharmacies serving approximately 450000 inhabitants, 232 recipients of ergotamine or sumatriptan had commenced OAC or ASA therapy after the start date of ergotamine or sumatriptan. After having satisfied eligibility criteria, 40% of the patients (n = 92) were included in the study population; 32 (35%) and 60 (65%) had been prescribed either OAC or ASA, respectively.

Of the 92 recipients, 79% were women and 21% were men; the mean age was 59.7 years (range, 28 to 77 years). The majority (64%) used ergotamine as the specific abortive migraine drug (Table 1). These characteristics did not differ between the OAC and ASA cohorts. The mean duration of anticoagulation therapy (time span between first and last prescription) was the only parameter in which a significant difference between the two cohorts was observed. The duration of treatment with ASA was approximately 2 1/2 years, compared with 1 year with OAC.

The overall intensity of ergotamine and sumatriptan use before anticoagulation therapy was comparable for the OAC and ASA cohorts (6.4 DDDs per month and 5.2 DDDs per month, respectively) (Table 2). During anticoagulation therapy, the overall intensity of abortive migraine drug use decreased by 53% from 6.4 to 3.0 DDDs per month for the OAC cohort, compared with a decrease of 15% from 5.2 to 4.4 DDDs per month for the ASA cohort ($P > .05$).

On an individual patient level, the reduction in therapeutic intensity, expressed as the *therapeutic in-*

Table 1.—Baseline Characteristics

	OAC Group (n = 32)	ASA Group (n = 60)	*P*
Sex			.80*
Women	25 (78)	48 (80)	
Men	7 (22)	12 (20)	
Mean age, y	58.5	60.5	.38†
(95% CI)	(54.5 to 62.6)	(58.0 to 63.0)	
Age, y			.41*
<55	10 (31)	14 (23)	
≥55	22 (69)	46 (77)	
Analgesic type			.75*
Ergotamine	19 (59)	40 (67)	
Sumatriptan	12 (38)	19 (32)	
Both	1 (3)	1 (1)	
Mean duration of anticoagulation, mo	13.7	30.3	.05†
(95% CI)	(4.7 to 23.2)	(23.5 to 37.0)	

Values are number (percentage) unless otherwise indicated. OAC indicates oral anticoagulation therapy; ASA, low-dose acetylsalicylic acid.
* Pearson χ^2.
† Student *t* test.

tensity reduction, was significantly greater in the OAC cohort (40%, compared with 4.7% in the ASA cohort; $P = .004$).

COMMENTS

In our study, we observed that on an individual patient level, coumarin treatment was clearly associated with a reduction in the therapeutic intensity of specific abortive migraine drug use in comparison with ASA treatment. This suggests that coumarin use reduced the frequency and/or severity of migraine attacks in the majority of the patients treated with the drug.

The mechanism by which these drugs exhibit a possible positive effect is still largely unknown. A reduction in platelet hyperaggregability[6,7] is unlikely to be an important factor; in our study, only a slight reduction in the therapeutic intensity of abortive migraine drug use was observed in the ASA cohort. A possible alternative explanation may be the ability of OAC to inhibit the production of nitric oxide, a molecule responsible for the pathogenesis of pain and vascular headaches.[12,13] Acetylsalicylic acid has no effect on the suppression of nitric oxide.

A few limitations to this study should not be ignored. In our study, we estimated changes in migraine frequency and severity by analyzing prescription data. The assumption was made that a prescription presented at the pharmacy correlates with consumption of the drug. It has been shown that consumption can be accurately estimated by means of complete prescription data for recipients of multiple prescriptions.[11,14] Our study included only those patients who presented multiple prescriptions for ergotamine or sumatriptan. Although there may be a degree of imprecision in this estimate, we believe that it is unlikely that there are significant differences in this degree of imprecision between the periods before and during OAC or ASA treatment or between the OAC and ASA cohorts.

In addition, information concerning the use of other analgesics, particularly OTC analgesics, was not available to us. However, in view of the large differ-

Table 2.—Therapeutic Intensity of Abortive Migraine Drug Use Before and During OAC or ASA Treatment

Therapeutic Intensity, DDDs Per Month (95% CI)	OAC Group (n = 32)	ASA Group (n = 60)
Before OAC/ASA	6.4 (3.2 to 9.6)	5.2 (3.6 to 6.7)
During OAC/ASA	3.0 (0.8 to 5.2)	4.4 (2.6 to 6.2)
Therapeutic intensity reduction*,%	40	4.7
	(23.0 to 57.0)	(−0.65 to +10.05)

OAC indicates oral coumarin/fenprocoumon therapy; ASA, low-dose acetylsalicylic acid; DDDs, defined daily doses.
* Therapeutic intensity reduction = 1 − (DDDs per month during/DDDs per month before) × 100%. $P = .004$, Mann-Whitney *U* test.

ences in abortive migraine drug use observed between the OAC and ASA cohorts during anticoagulation treatment, we think this limitation did not bias our findings.

Similar to other epidemiologic studies investigating the relationship between migraine and stroke,[7,8] the majority of our study population included elderly patients with migraine. As a result, it could be argued that the reduction in migraine analgesic consumption in some patients may have been related to the age-related decline in migraine attacks. In view of the comparable age features within the OAC and ASA cohorts, a comparable reduction in abortive migraine drug consumption in the ASA cohort would be expected if age was a predominant factor. Similar to the findings of Morales-Asin et al,[5] we can confirm that a reduction in abortive drug consumption during coumarin therapy was more likely an effect of OAC treatment.

In view of the vasoconstrictive properties of ergotamine and sumatriptan, physicians may have generally been more reluctant to prescribe these drugs to migraineurs recently having experienced cardiovascular or thromboembolic complications, which are the indications for coumarin or ASA treatment.[15-17] In order to overcome this problem of "confounding by contraindication," we included ASA users as the control group. Despite these limitations, we feel that the observed reduction in therapeutic intensity of abortive migraine drug use during coumarin therapy is a true phenomenon and unbiased.

In conclusion, we have shown that treatment with OAC when compared with ASA can lead to a significant reduction in specific abortive migraine drug use in the majority of the patients treated. This suggests that patients treated with coumarin derivatives experience a reduction in the frequency of migraine attacks and, possibly, an amelioration of their migraine. Although our results could not highlight the potential clinical significance of these effects, they do, however, add to the existing evidence that coumarin therapy may offer beneficial effects to the migraineur.

Our findings, as well as those of others, justify the need for a controlled clinical trial to further establish the effects of coumarin therapy on migraine severity and its possible role in the prophylactic management of patients suffering from migraine.

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