Improving the quality of oral anticoagulant therapy

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CHAPTER 1

INTRODUCTION

Introduction

Oral anticoagulants have been of interest to the medical profession since the time of Hippocrates (c. 460 BC–380 BC) himself. Hippocrates advocated removal of part of the blood or the administration of white wine to make the blood "thinner", especially in women with little menstrual blood flow [1]. Some extracts of plants were also advocated as "blood thinners".

Galen (131-201 AD) agreed with Hippocrates and stated that blood could be too "fibrous" in some patients and advocated induction of diarrhoea by an extract of rhubarb to make the blood "thinner" [2]. Bloodletting, leech bleeding, acid fruits and clear wines were also recommended.

Later in history barber-surgeons resorted to outlandish remedies such as oral administration of mummy powder to thin the blood [3]. In 1751, Theophile de Bordeu claimed to have studied many of the blood thinners that had been suggested over the centuries, and found that not one of them actually worked [4]. His views were widely believed and instead of chemical "thinners" physicians resorted to blood letting.

Discovery of coumarin anticoagulants

The history of the discovery and development of coumarin anticoagulants started in 1921 when a farmer in North Dakota, USA, dehorned 80 calves which subsequently all bled to death. This was typical of a serious hemorrhagic diathesis of cattle that became epidemic in 1921. The first scientific report about it appeared in 1924 [5]. Frank Schofield found that cattle bled only when they were fed sweet clover (Melilotus Alba or Melilotus officinalis) that had become mouldy. During a serious drought in the Midwest of the USA farmers were only able to grow sweet clover in the poor soil, and surprisingly cattle would eat the plant despite its bitter taste (which was due to its coumarin content). After some experiments Schofield decided that the mould, usually aspergillus, induced the sweet clover to produce a toxin. He recommended that prevention of the disease required that the farmers disposed of the mouldy sweet clover and replaced it with clean sweet clover. Bleeding episodes had to be treated with whole blood transfusions.

The disease continued though the 1920s and early 1930s. In 1933, Karl Link embarked on a study of the cattle disease at the University of Wisconsin and in 1939 his team crystallized the anticoagulant material [6]. Almost a year later the structure was identified and the chemical was synthesized [7]. The substance which Link named "dicumarol" had no anticoagulant effect when added to a blood specimen.

In 1941, the Mayo Clinic conducted a study of the prevention of postoperative thrombosis by treating patients with dicumarol immediately after the surgical operation. The reduction of postoperative

thrombosis was so dramatic that a paper was published within 3 months [8]. Soon, dicumarol was used throughout the world to prevent and to treat thromboembolic problems [9]. In 1942 and 1943, it was found that vitamin K was effective against the oral anticoagulant when administered in doses large enough to overcome the anti-vitamin K effect [10].

Link's group prepared over 150 analogs of dicumarol looking not so much for a better anticoagulant for human patients but rather for a more effective rodenticide. In 1948, a compound was obtained which was ten times more potent than dicumarol and, unlike dicumarol, water soluble. To acknowledge the financial help of the Wisconsin Alumni Research Foundation (WARF) the compound was named "Warfarin".

In 1955 President Dwight Eisenhower of the United States became one of the first famous patients on warfarin when he was treated with this drug at a dose of 35mg/week after a myocardial infarction [11]. He would stay on this treatment until his death and it was only suspended for an operation for a bowel obstruction and a cholecystectomy. The treatment would not protect him against further heart attacks and a stroke.

Warfarin has since then not only become used as a highly effective rodenticide but also as the major oral anticoagulant for human thromboembolic diseases throughout the world.

Action of coumarin anticoagulants

Coumarin anticoagulants induce anticoagulation by inhibiting vitamin K-dependent γ-carboxylation of the glutamine (Glu) residues on the N-terminal terminals of the vitamin K-dependent coagulation proteins (Factor II, VII, IX and X, protein C and S) into γ-carboxy-glutamate (Gla) residues [12]. The process of γ-carboxylation allows the coagulation factors to undergo a conformational change in the presence of calcium ions, a necessary requirement for binding to phospholipids on the surface of blood platelets and endothelial cells at the site of injury. Vitamin K-dependent γ-carboxylation has been shown to require molecular oxygen, carbon dioxide and the fully reduced form of vitamin K quinone, vitamin K hydroquinone. Because the normally occurring forms of vitamin K are quinones, the vitamin must, prior to catalyzing the γ-carboxylation reaction, be reduced to the hydroquinone by various reductases present in the tissues that synthesize γ-carboxyglutamic acid-containing proteins. Two different pathways can participate in the reduction of vitamin K quinone to its hydroquinone. Vitamin K hydroquinone is the active cofactor form of the vitamin K for the carboxylases and is converted into vitamin K epoxide in the process of γ-carboxylation [13]. Once formed, vitamin K epoxide can, after enzymatic reduction, be recirculated as cofactor for the carboxylase.

Vitamin K epoxide reductase and vitamin K quinone reductase are the targets of coumarin anticoagulants such as warfarin (Coumadin®), acenocoumarol (Sintrom®) and phenprocoumon (Marcoumar®). Inhibition of this pathway by the coumarins is essentially reversible by vitamin K

Pharmacokinetics of coumarin anticoagulants and interactions

The most frequently used coumarin anticoagulants are warfarin (Coumadin®), acenocoumarol (Sintrom®) and phenprocoumon (Marcoumar®). Warfarin is most commonly used in the world, and predominantly in the English-speaking countries and Scandinavia, while acenocoumarol and phenprocoumon are used mainly in Western Europe. The mechanism of action is similar for the three compounds but they differ in pharmacokinetics. Phenprocoumon is the longest-acting with a half-life of around 140 hours, with a half-life for warfarin of around 40 hours and only 11 hours for acenocoumarol. All three have a rapid absorption from the gastrointestinal tract with maximal blood concentration reached in approximately 90 minutes [14]. The presence of food slows the rate of absorption but does not affect bioavailability. All three drugs are metabolized in the liver by the cytochrome P450 system and the metabolites are predominantly excreted through the kidneys.

Because coumarin anticoagulants reach their effect through inhibition of the vitamin K cycle, the intake of vitamin K through the diet will affect the level of anticoagulation. Many important interactions exist with other drugs, some increasing the sensitivity of the patient to coumarins, other impacting on the metabolism of the coumarin drugs themselves [15]. Finally, the effect of the coumarin anticoagulants is also affected by the metabolism of the body and by other illnesses.

Monitoring of the coumarin anticoagulant effect

Coumarin anticoagulation needs to be strictly monitored because of the narrow therapeutic area between under- and over-anticoagulation. In case of under-anticoagulation the patient is at risk for thromboembolic complications and in case of over-anticoagulation there is an increased risk of severe bleeding problems. Frequent monitoring is necessary to adjust the dose in response to different interactions by food, drugs and illness.

The laboratory test most used for the monitoring of coumarin anticoagulation is the Prothrombin Time (PT) introduced by A.J. Quick in 1935 [16]. The PT is responsive to the tissue factor clotting pathway and is prolonged by a reduction in three of the vitamin K-dependent clotting factors (II, VII and X). It measures the clotting time of citrated plasma after the addition of thromboplastin, a tissue extract which contains both Tissue Factor and the phospholipids necessary to promote the activation of Factor X by Factor VII. Varying test procedures and, predominantly, differences in the thromboplastins are responsible for important discrepancies in the results for the same test plasmas in different laboratories and hospitals [17]. Furthermore, the prothrombin time test results can be given in different forms such as a prothrombin time in seconds, prothrombin time ratio, prothrombin index, and prothrombin activity in percentage. These variations made it virtually impossible for a patient to be followed by more than one laboratory throughout his treatment period because comparisons between different laboratories led to dangerous fluctuations in the degree of anticoagulation.

In 1983 the World Health Organization (WHO) introduced a system of PT standardi-

zation using the International Normalized Ratio (INR). In this system all commercially available thromboplastins are calibrated against an international WHO standard and their sensitivity against this standard is expressed as an International Sensitivity Index (ISI). This way, every prothrombin ratio (prothrombin time of the patient in seconds / prothrombin time of normal population in seconds) measured by a calibrated thromboplastin can be converted into an INR, according to the formula 'INR = observed prothrombin ratio^{ISI}'. Through this formula the prothrombin ratio is expressed as if the original test had been done with the WHO reference thromboplastin [18].

The introduction of the INR has not only provided a common scale for oral anticoagulation but has also facilitated recommendations for optimal therapeutic ranges in INR [19-24]. These ranges are the result of a coordinated attempt by laboratory physicians and clinicians to achieve greater effectiveness and safety of oral anticoagulation. The introduction of the INR has permitted segmentation of the previous blanket therapeutic range, thus providing greater margins of safety in dosage from haemorrhage and thromboembolic complications in specific clinical states[20]. Although the 2.0 – 3.0 INR (lower intensity) range is now generally recommended for most clinical situations, in some conditions more intense (INR 3.0 – 4.0) or very low intensity (INR below 2.0) treatments are advised [19-24]. In the Netherlands the target ranges put forward by the Dutch Federation of Anticoagulation Clinics (Federatie Nederlandse Trombosediensten, FNT) are 2.5 – 3.5 and 3.0 – 4.0 [26].

In the Netherlands oral anticoagulant treatment is monitored by a system of regional anticoagulation clinics that are responsible for the collection of blood samples, the determination of the PT/INR and the prescription of dosage schedules for all out-patients on oral anticoagulant therapy [27-28]. This specialized system serves more than 95% of all Dutch patients on oral anticoagulant therapy at any given time, which comes to around 300,000 patients per year. Despite this highly specialized organization, an intensive laboratory quality control and dose-adjustments by experienced physicians with the aid of modern computer algorithms, the intensity of the anticoagulation is nevertheless outside of the target INR range for considerable accumulated periods of time for a substantial number of patients leading to thrombotic or hemorrhagic complications [29-32]. Nevertheless, the presence of a system of dedicated anticoagulation clinics has been proven in several countries to increase the quality of oral anticoagulant therapy and reduce the risk of these complications [33-36].

In the last years the concept of patient self-management of oral anticoagulant treatment has come to the foreground in an attempt to increase both the quality of the treatment and the quality of life as this treatment modality liberates the patient from the burden of frequently having to go to a general practitioner, laboratory, hospital or anticoagulation clinic for a venous puncture in order to obtain the PT/INR necessary for dose monitoring and dose adjustments. Originally point-of-care devices were developed for use by dedicated health professionals but this evolved first to patient self-testing with the dose management done by physicians, and afterwards to full patient self-management. In the countries where this system was first established, e.g. Germany, Scandinavia and the United States, this led to an improvement in the quality of the oral anticoagulant treatment [37-47]. As the standard of oral anticoagulant care in the Netherlands was already high

compared to the surrounding countries and because of the presence of a highly structured system of anticoagulant care in the form of the regional anticoagulation clinics, there was no urgent need for the implementation of patient self-testing and self-management in this area of medicine. This can explain the delay in the implementation of this mode of treatment in the Netherlands [48].

Indications for coumarin anticoagulation therapy

Coumarin anticoagulant treatment is given for the treatment and prevention, both primary and secondary, of thromboembolism. Treatment can be for short or long-term duration, or even for life-long duration.

Venous Thrombosis (VT), which combines deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common cause of morbidity and mortality [49-50]. The annual rate of DVT in the general population has been estimated at between 48 and 162 per 100 000 population and the rate of PE has been estimated at 23-51/100 000 per year [50-52].

Although venous thromboembolism is common and potentially lethal, this outcome is largely preventable. Coumarin oral anticoagulants have been shown to be effective in preventing DVT and PE mortality, and subsequently these drugs have also been demonstrated to be effective thromboprophylactic agents in a large number of clinical trials [53]. The short-term objectives for anticoagulant therapy of existing VTE are cessation of thrombus extension, prevention of symptomatic and fatal PE, and reduction in leg or chest symptoms associated with the initial event. Longer-term objectives include prevention of recurrence after the initial thrombotic process that has been suppressed, reduction in the risk of post-thrombotic syndrome, and prevention of thromboembolic pulmonary hypertension.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is rare before the age of 60 and rises in prevalence with increasing age, so that over 8% of individuals older than 80 years have AF [54]. The risk of stroke is increased approximately five-fold in the average patient with AF, and about 18-

fold in patients with AF and rheumatic mitral stenosis[55]. The Framingham study has estimated that approximately 24% of strokes in patients over 80 years of age are attributable to AF [54]. The efficacy of oral anticoagulants in AF has been evaluated in several large studies [56-60]. The risk reduction for stroke with the use of oral anticoagulants was confirmed in all studies, and exceeded the effect obtained by aspirin [56-60].

The place of oral anticoagulants in secondary and primary prevention of myocardial infarction and coronary death has been contentious and several trials have looked at this issue. The intensity of the anticoagulant treatment and its monitoring were of major importance to balance the net benefits on vascular death, vascular events and recurrent myocardial infarction, especially in earlier studies. Later studies have shown a clear benefit of the coumarin anticoagulants in terms of mortality and reinfarction, again with a benefit larger than that conferred by aspirin [61-63].

Despite improvements in valve design and monitoring of anticoagulant therapy, systemic embolism and bleeding remain serious complications in patients following heart valve replacement. In addition, systemic embolism and stroke are important complications in patients with valvular heart disease. Although there are no randomized trials comparing oral anticoagulation with no treatment in such patients, it is generally agreed that anticoagulant therapy can reduce the frequency of systemic embolism and is indicated for life in patients with mechanical prosthetic valves, in patients with tissue valves if associated with atrial fibrillation or a history of thromboembolism, and in patients with valvular disease who have additional risk factors for embolism [64-66].

Oral anticoagulants have been used for prevention of ischemic stroke for more than 50 years but their optimal application remains unclear and increasingly controversial. Clinical trials are in the process of testing different intensities of anticoagulation, sometimes in combination with antiplatelet drugs, in different patho-etiologic subgroups of patients with threatened stroke [67]. Combinations of very low intensity oral anticoagulation with aspirin have received much attention lately in an effort to balance efficacy with the high risk of haemorrhage [68].

Hemorrhagic complications of coumarin anticoagulant therapy

The most important complication of any anticoagulant therapy is the occurrence of haemorrhages, which may be minor or severe, and potentially fatal. The risk of severe bleeding caused by oral anticoagulation is around 1.8 – 2.4%/year for patients within the target INR range [25, 69-75]. The duration of the anticoagulant therapy and the intensity of anticoagulation are critical determinants of the risk of anticoagulant-related bleeding. These figures show a clear rise with increasing age above 60 and with increasingly high INR values. The risk of bleeding complications is also increased by combining oral anticoagulant therapy with aspirin [74-75], or in patients with co-morbidity, especially cardiac, renal, hepatic and cerebrovascular disease.

In an effort to reduce the percentage of hemorrhagic complications without loss of efficacy of the treatment, much effort has gone in refining both the optimum duration and optimum intensity of oral anticoagulant therapy [76-79], and in improving overall management of this treatment to prevent both over- and under-anticoagulation [80-87].

Aims and outline of this manuscript

The studies outlined in this thesis have been performed to indicate ways in which oral anticoagulant treatment can be made more efficient, more safe or even more pleasant, i.e. less intrusive, for the patient.

One way to improve the quality of oral anticoagulant treatment is to look at the drugs which are used for this treatment. Coumarins have been the mainstay for oral anticoagulation for decades and differ mainly in their plasma half-life. In the past comparisons as to treatment quality have been done between the short-acting acenocoumarol (Sintrom®) and the medium-long-acting warfarin (Coumadin®) favouring the longer-acting coumarin [88].

In chapter 2 we describe the results of a retrospective comparison between two patient groups (n=288) matched patient by patient for indication for oral anticoagulant therapy, age, sex, date of start of treatment, and duration of treatment, but differing in the coumarin used, with half on acenocoumarol (Sintrom®) and the other half on phenprocoumon (Marcoumar®). Treatment quality was determined by the time-in-range, i.e. the percentage of time the patients spend within the predefined target INR range. The results from this comparison were validated by a more limited analysis of patients of another anticoagulation clinic to discount the possible effects of bias through increased experience with one of the two coumarins studied.

In chapter 3 we return to the comparison between the short-acting acenocoumarol and the long-acting phenprocoumon. Using data from six anticoagulation clinics in the Netherlands, we performed a retrospective cohort study to compare the relative control

and stability of the INR among patients taking either acenocoumarol or phenprocoumon. We were also interested in learning whether there were consistent differences in manner in which anticoagulation was managed among the six clinics. For this study we made use of the cross-section of the files method analyzing more than 22 000 patients.

Another way to improve the quality of oral anticoagulant therapy is to hand over the monitoring of the treatment to the patients themselves, as is done with for example diabetes care. This patient self-management was tested in other countries where, unlike the Netherlands, no highly structured oral anticoagulant care was available, and in these countries a clear benefit was seen.

In chapter 4 we present the results of a large randomized prospective two-centre study which analyzed the effects of patient self-testing, full patient self-management and patient training on the quality of oral anticoagulant care versus the standard of care delivered by the Dutch system of anticoagulation clinics.

Within the multi-centre randomized study performed by two Dutch anticoagulation clinics, designed to study the effect on treatment quality (time within target range) of different modalities of patient self-management, we looked at the effect of increased patient education, self-monitoring of the INR and full patient self-management (INR monitoring and dosing of the OAT) on the Quality of Life of the patients. This was done with the aid of a written questionnaire (32 questions) at baseline, and after 26 weeks. We compared the results after 26 weeks to those at baseline, as well as between groups. The results of this study are presented in chapter 5.

Oral anticoagulant therapy is heavily influenced by co-medication. Painkillers are especially important in this regard because acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAID) increase the bleeding tendency by interfering with platelet aggregation. Paracetamol is routinely advocated by the anticoagulation clinics as a safe painkiller and anti-fever drug. Some disquiet arose when there were indications in the literature that paracetamol could increase the INR [89]. The major problem with those studies was that they were of an observational nature, and therefore could not distinguish between an effect of the drug (paracetamol), or by the indication for which it was taken (minor disease), i.e. confounding by indication was not ruled out.

In chapter 6 we describe the results of a double blind randomized controlled trial in which 31 out-patients on coumarin oral anticoagulant therapy with phenprocoumon without an indication for paracetamol were randomised between placebo, 1500mg paracetamol daily or 3000mg paracetamol daily for 14 days during the stable phase of coumarin therapy. INR values were measured at days 1, 8, 15, 22 and 29.

When we try to improve the quality of oral anticoagulant treatment we think in terms of time-in-range, of improving the percentage of time the patient spends within predefined INR target ranges in an effort to balance efficacy, i.e. the need to prevent thrombosis, with the risks of over-anticoagulation, i.e. the risk of bleeding complications. The INR target ranges are in themselves set up to balance these opposing risks.

In chapter 7 we present the results of an analysis of the quality of the oral anticoagulant therapy for the initial venous thrombosis and its relationship with recurrence of thrombosis in subsequent years in the Leiden Thrombophilia Study (LETS), a population-based case-control study on risk factors for venous thrombosis, in which many genetic

and acquired factors have been investigated previously. This study was carried out in an effort to identify the critical INR levels to prevent recurrence of thrombosis.

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