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Out of hospital anticoagulant therapy in patients with acute pulmonary embolism is frequently practised but not perfect

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ABSTRACT

Introduction: Traditionally, patients with pulmonary embolism (PE) are treated in-hospital until they reach an adequate international normalized ratio (INR). Analogous to patients with a deep venous thrombosis, therapy with low-molecular-weight heparin facilitates out of hospital treatment of PE. We retrospectively analysed the current practice of early anticoagulant therapy in 86 acute PE patients with emphasis on the occurrence and safety of outpatient treatment.
Methods: Data were collected from two large regional teaching hospitals and from a specialized anticoagulation clinical, where patients were followed in the period after hospital discharge. The course of hospitalization and LMWH transitioning therapy and the quality of treatment in the first three months after diagnosis were compared between patients discharged before and patients discharged after reaching adequate INR.
Results: Forty-four patients (51.2%) were discharged early, before reaching an adequate INR, and 42 patients (48.8%) were discharged after reaching adequate INR. Early discharged patients needed more time to reach adequate INR compared to other patients (13 versus 6 days). In 28 patients (32.6%), the LMWH transitioning therapy was stopped prematurely; 21 patients were from the early discharged group. During the first 3 months, the mean individual times below, in and above the INR range were equal between the two groups.
Conclusion: Enhanced compliance to existing guidelines and tools, and further development of guidelines, with focus on intensification of monitoring of INR values in an outpatient setting and preventing premature discontinuation of transitioning therapy, are warranted for a safe and early discharge of stable patients with PE.

Introduction

Where home treatment is a standard modality for patients with deep venous thrombosis, anticoagulation therapy for patients with PE is traditionally initiated in a hospital setting. In accordance to both international [1,2] and Dutch [3–5] protocols, treatment of nonmassive PE comprises subcutaneous injection of low-molecular-weight-heparin (LMWH) transitioning therapy and treatment with one of the registered vitamin K antagonists acenocoumarol, warfarin or phenprocoumon for at least 3 months. There are numerous factors influencing the international normalized ratio (INR) such as dietary Vitamin K [6,7] variable medications [8,9], malignancy [9,10], age [10,11], Vitamin K epoxide reductase (VKORC1) gene polymorphism [12], and patient education and compliance [13,14]. The setting of oral anticoagulant therapy (OAT) monitoring is also an important factor influencing its quality, where study results seem to favour outpatient control by specialized anticoagulation clinics [15].

LMWH transitioning therapy to OAT is discontinued when INR is stable and two consecutive INR measurements are >2.0 after a minimum of 5 days. The five day limit is based on the fact that the antithrombotic effect of OAT, caused by depletion of factors II and X, takes 4 to 6 days to occur. A fast increase in INR after the start of OAT mainly reflects a decrease in FVII activity, and does not indicate proper anticoagulation. At the same time, vitamin K antagonist also inhibit the formation of the inhibitors of coagulation Protein C and S, thereby

Abbreviations: PE, pulmonary embolism; INR, international normalised ratio; LMWH, low-molecular-weight heparin; OAT, oral anticoagulant therapy; TBR, Time below range (INR<2.0); TIR, Time in therapeutic range (INR 2.0 – 3.5); TAR, Time above range (INR>3.5); TcAR, Time critically above range (INR>4.5); ANOVA, analysis of variance; SAE, serious adverse events; SD, standard deviation; VTE, venous thromboembolism.

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even increasing the risk on thrombosis if LMWH transitioning therapy is stopped before OAT has generated its anticoagulant effect [16].

The above mentioned guidelines do not specify criteria for discharge of patients with PE after hospitalisation. Consequently, it is not surprising that discharge behaviour differs between physicians. A study of Caprini *et al* [17] shows that most patients with PE are discharged after discontinuation of transitioning therapy (with LMWH or unfractionated heparin). Nevertheless patients with PE are also frequently discharged early with LMWH transitioning therapy to OAT still ongoing.

The aim of the present study is to describe the current practice of early anticoagulant therapy in patients with acute PE in two large teaching hospitals in the Netherlands.

Materials and Methods

Patients

We retrospectively analyzed the data of consecutive outpatients, who were admitted with suspected PE at the St. Antonius Hospital, Nieuwegein or Diakonessenhuis, Utrecht (two large teaching hospitals in the centre of the Netherlands) between January 2005 and July 2007. Diagnosis of PE was confirmed with an intraluminal filling defect on spiral CT or pulmonary angiography, a high probability ventilation-perfusion lung scan, or a non-diagnostic lung scan with a deep venous thrombosis shown by compression ultrasonography of the legs in combination with a high clinical probability of PE.

Eligible patients were selected out of the computerized files of the Thrombosis Service Utrecht. Patients were followed for a period of three months and data on INR values and clinical outcome were documented. INR values were collected from the laboratories of the hospitals and the Thrombosis Service Utrecht. Information about patient characteristics and the clinical outcome was obtained from clinical reports or from additional information of the Thrombosis Service Utrecht. Patients were excluded when they received initial treatment with only LMWH, when they had OAT in the month preceding PE diagnosis or when it was necessary to stop the OAT during the follow-up period in case of surgery.

OAT monitoring

OAT was initiated in the hospital setting and controlled by the treating physician. Monitoring after discharge was provided by specially trained physicians and nurses of the Dutch anticoagulation clinic Thrombosis Service, Utrecht. At the Thrombosis Service, OAT dosing schedules were determined with the aid of the computerized dosing program TRODIS (version II in 2005; version III in 2006 and 2007). This program evaluates the stability of INR values and, based on a dosing algorithm, proposes a dosage in approximately 50% of all cases, of which half are subsequently overruled by the physicians or nurses upon evaluation.

Determination of INR

In both hospitals and at the Thrombosis Service Utrecht venous blood was collected in a 3.2% citrate solution and plasma was obtained by centrifugation. The INR of the prothrombin time was determined with the Hepatoquick reagent (Diagnostica STAGO/ Roche Diagnostics, France) with an International Sensitivity Index of 0.88-0.93, using either a STA-R or a STA-R Evolution coagulometer (Diagnostica STAGO/ Roche Diagnostics, France). The frequency of INR measurements was variable. In hospital, INR measurement was according to the responsible physician. After discharge, INR measurement was according to the Thrombosis Service Utrecht. Time needed to reach adequate INR was calculated in days. INR was defined adequate when two consecutive measurements were >2.0, measured on day 4 and 5 or later. The day of diagnosis PE was defined as day 0.

Time in therapeutic range (TIR)

Day-tot-day INR values were calculated using the linear interpolation model [18]. With this model, the INR values on days between the INR measurements are calculated by assuming a linear fashioned change between each measurement. With the calculated INR values the individual time spent below, in and above range was calculated for the first, second and third month after diagnosis. In the Netherlands, the therapeutic INR range for patients with PE is set on 2.0-3.5. This range is somewhat extended as opposed to the internationally accepted range of 2.0-3.0. The main reason for this extension is to escape under-anticoagulation.

Study outcomes

Primary objective was to study the differences in location (in or out of hospital) and in quality of current practice of early anticoagulant therapy in patients with acute PE. Quality of early anticoagulant therapy was evaluated using the percentage of patients with inadequate LMWH treatment, time and number of INR measurements needed to reach adequate INR and the time spent below (INR<2.0), in (INR 2.0 – 3.5), above (INR>3.5), or critically above range (INR>4.5) [19] during the first three months of OAT. Secondary study outcomes included mean duration of hospitalisation and number of clinical serious adverse events (SAE), including major bleeding, recurrent VTE or death [20].

Statistical analysis

Descriptive statistics were used to describe patient characteristics. One-way ANOVA test was used to test for differences in mean values between groups. Fisher's Exact test was used to test for differences in frequencies. For all analyses, a two-tailed p-value of less than 0.05 was considered to indicate statistical significance. Values are expressed as either number (percentage) or as mean ± standard deviation. When lost to follow-up, all available data until the day of loss were included in the analysis. Statistical analysis was performed using the Statistical Package for Social Science (version 15; SPSS; Chicago, IL, USA).

Results

Characteristics of study population

Between January 2005 and July 2007, 86 patients were admitted for primary PE and included in this study. One patient was lost to follow-up in a period of three months. All patients received LMWH transitioning therapy and acenocoumarol from the day of diagnosis. Four patients crossed over from acenocoumarol to phenprocoumon during the second or third month of treatment (day 41, 61, 63, 88, respectively), because of poor control with acenocoumarol. Twelve patients (14%) received OAT despite the presence of a known malignancy. The patients' characteristics are shown in Table 1.

Hospital Discharge

The mean length of hospital stay was 6.9 ± 4.3 days (Table 2). Forty-four patients (51.2%) were discharged before reaching an adequate INR after a mean 4.5 ± 3.8 days. These patients were considered as early discharged (group 1). After a mean 9.4 ± 3.2 days, the remaining 42 patients (48.8%) were discharged after reaching an adequate INR (group 2). Of these 42 patients, 16 patients were discharged on the day of or the day after reaching an adequate INR. From the remaining 26 patients, 10 patients had substantial co-