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<th>Warfarin prevalence, indications for use and haemorrhagic events</th>
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<tr>
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</tr>
<tr>
<td>Publication date</td>
<td>2007-03</td>
</tr>
<tr>
<td>Type of publication</td>
<td>Article (peer-reviewed)</td>
</tr>
<tr>
<td>Rights</td>
<td>© Irish Medical Journal 2007</td>
</tr>
<tr>
<td>Item downloaded from</td>
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Abstract

Warfarin, the standard oral anticoagulant drug used in Ireland, is a widely prescribed medication, particularly in the elderly. In the HSE Mid-Western area, a wide audit was undertaken over a 12-month period to examine the prevalence and indications for warfarin use and haemorrhagic complications associated with the drug. Every patient receiving warfarin therapy over a 12-week period was included (2564). The age standardised rate varied from 0.09% of 35-39 year olds to 61.1% of 80-84 year olds. Acute intracranial hemorrhage was the most common indication (54%) in patients attending the Mid-Western Regional Hospital anticoagulation clinic. The annual cumulative incidence of adverse haemorrhagic events in the patient population (1000 standardised to Irish census 2002). In the very elderly (>85 years), the rate declined to 16.6%. The incidence of major and minor haemorrhagic events per INR=5.0 episode was 1.3% and 15.3% respectively. The most common sites of haemorrhage were gastrointestinal (39%) and genitourinary (27%). No fatal or intracranial haemorrhage relating to episodes of over-anticoagulation were reported during the audit period. The most frequent reason for over-anticoagulation was drug interaction (43%). In 74% of patients, the elevated INR was reversed by omitting or reducing warfarin dose. In 17% of cases, vitamin K was administered. Only 3% of incidents were treated with fresh frozen plasma or prothrombin complex concentrates.

Introduction

Warfarin is effective in the prevention of venous thromboembolism, thromboses in patients with heart valve prostheses, embolic strokes in patients with chronic atrial fibrillation and cerebrovascular disease. It is also of proven benefit in patients with pulmonary embolism and as secondary prophylaxis following myocardial infarction. Otherwise, warfarin is associated with a significant incidence of serious haemorrhage. In a review of observational studies, average annual rates of fatal, major and minor/major haemorrhages were 0.8, 4.9 and 15% respectively. The incidence of haemorrhage in warfarinised patients is directly related to the adequacy of control. Systems for the control of warfarin are evolving and becoming more sophisticated. Quality improvements in systems include the increasing use of computerised dosing, specialist nursing input into monitoring patients and the use of near patient testing for coagulation. These have been initiated with set protocols recommended by the British Committee for Standards in Haematology.

The delivery of care to warfarinised patients in the HSE Mid-Western area has undergone major changes between 1999 and 2002. During this time a computerised nurse led anticoagulation clinic replaced the more traditional physician led system. This was achieved with cross-disciplinary co-operation and resources from the HSE Mid-Western area and the national partnership process. The audit was undertaken after this period of change.

This audit aimed to establish the age related incidence of warfarin use in the HSE Mid-Western area and determine the frequency of indications for its use. Causes of over-anticoagulation were examined which we hope will aid clinicians in the management of these patients. Warfarin is worrisome as it is associated with a significant incidence of serious haemorrhage. In a review of observational studies, average annual rates of fatal, major and minor/major haemorrhages were 0.8, 4.9 and 15% respectively. The incidence of major and minor haemorrhagic events per INR=5.0 episode was 1.3% and 15.3% respectively. The most common sites of haemorrhage were gastrointestinal (39%) and genitourinary (27%). No fatal or intracranial haemorrhage relating to episodes of over-anticoagulation were reported during the audit period. The most frequent reason for over-anticoagulation was drug interaction (43%). In 74% of patients, the elevated INR was reversed by omitting or reducing warfarin dose. In 17% of cases, vitamin K was administered. Only 3% of incidents were treated with fresh frozen plasma or prothrombin complex concentrates.

Methods

Identification of warfarinised patients (laboratory computer records)

To quantify patients on warfarin within the borders of the HSE Mid-Western area, hospital laboratory computer records were interrogated in its laboratories, i.e. Mid-Western Regional Hospital Limerick, St Johns Hospital Limerick, Ennis and Nenagh General Hospitals. We achieved this through COGNOS, a data extracting software package for iLAB, the laboratory information system. This number was quantified from a 13-week period, August 1st 2002 to October 31st 2002, a timeframe we deemed to be the maximum review interval for a patient on warfarin. Patients who had an INR>5.0 for occasions over 2 weeks or more were deemed to be on warfarin unless there was a defined exclusion. For example, a patient was deemed to be on warfarin if they were female, had an INR between 0.9 and 1.5, and were receiving an antibody to a virus or a disease, e.g. haemolytic disorders, disseminated intravascular coagulation (DIC) or liver abnormalities were excluded. To ensure completeness of the computerised record and to allow the denominator of the population of the HSE Mid-Western area to be accurately utilised, laboratories on the borders of the HSE Mid-Western area (Tralee, Clonmel, Cashel, Galway, Mallow and Waterford) were contacted. This allowed us to establish whether any patients, with Mid-Western Area addresses, had their INR monitored outside our region. Patients whose INR was monitored exclusively by near patient testing (Coagucheck) were determined by liaison with Roche Diagnostics and their customers. The resulting data was analysed and age standardised (Irish population standard) using the direct method.

Identification of over-anticoagulated patients (laboratory computer records)

Over-anticoagulated patients were quantified from August 1st 2002 to August 1st 2003. Patients with an INR=5.0 episode in the 12-month audit period were identified from computer records using COGNOS, in HSE Mid-Western area hospital laboratories, to determine the prevalence and incidence of haemorrhages in such instances. An INR of five or above was chosen because INR values greater than five have shown a consistent increase in haemorrhagic events.

Investigation of over-anticoagulated patients and categorisation of associated haemorrhagic events

Patients with INR=5.0 were linked to accident and emergency attendances or inpatient/clinic records. Anticoagulation nurses and haematology medical staff examined the casualty record and hospital chart. We examined the record to determine the suspected primary cause of loss of INR control, action taken for its reversal and if any blood loss was transfused. We also audited the use of blood products, vitamin K and stopping warfarin as means of reversal of over-anticoagulated patients.

Results

The number of patients estimated to be receiving warfarin within the HSE Mid-Western area was 2564. As expected, the age standardised rates (Table 1) rose sharply with age and in-patient age range of 80-84 it reached a maximum of 6.1% of the population (61/1000 standardised to Irish census 2002). In the very elderly (>85 years), the rate declined to 3.6% (36.5/1000).

Table 1 Age standardised prevalence rates of warfarin use in the HSE Mid-Western Area

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number on warfarin</th>
<th>HSE Mid-West area population</th>
<th>Ireland population</th>
<th>Age specific rates per 1000 people mid-west</th>
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<td>20-24</td>
<td>12</td>
<td>35241</td>
<td>128334</td>
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Warfarin Prevalence, indications for use and haemorrhagic events
The most common indication for treatment was atrial fibrillation (54%). The ratio of male to female patients was 1.4:1. The average age of the patient was 66.5 years.

The number of patients presenting with INR=5.0 episodes in the 12-month audit period was 463. Detailed information was available on 357 of these episodes from which confirmation of warfarinisation was made in 307 cases. Information on the remaining 136 episodes was unavailable due to missing/non-documentation of over-anticoagulation events and the inability to access some community or general practitioner records.

Table 2 shows the suspected primary cause of INR=5.0 cases, the most common being drug interaction (43%).

Within the audit period, 51 patients (16.6%) who presented with an INR=5.0 experienced episodes of haemorrhage. Of these 47 (15.3%) had a minor haemorrhage while 4 (1.3%) had a major haemorrhage. No fatal haemorrhage relating to over-anticoagulated patients was reported during the audit period. The most common sites of haemorrhage were gastrointestinal (25.9%) and cutaneous (27.5%). Other types of haemorrhage discovered in over-anticoagulated patients were bruising/haematoma of soft tissue (11.8%), epistaxis (7.8%), haemoptysis (5.9%), gingival/oral mucosal bleeding (4.0%), and more than 1 of the above recorded (8.8%).

Table 3 shows the suspected primary cause of INR=5.0 cases, the most common being drug interaction (43%).

Table 4 details the action taken to counteract episodes of over-anticoagulation. The most frequently used method of INR reversal was warfarin dose omission/reduction (74%).

Information not available on 7 patients whose INR was tested in laboratories outside the borders of the HSE-Western area.

Discussion

Reasons for warfarin therapy in patients attending the Mid-Western Regional Hospital clinic are summarised in Table 2. The most common indication for treatment was atrial fibrillation (54%). The ratio of male to female patients was 1.4:1. The average age of the patient was 66.5 years.

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Discussion

Due to its narrow therapeutic index and its pharmacokinetic and pharmacodynamic properties, warfarin is highly susceptible to interactions with other drug components. The high incidence of interacting medication (43%) as a cause of loss of INR control needs to be addressed. The most common clinical picture associated with drug induced alterations in INR was the treatment of exacerbations of chronic obstructive pulmonary disease and infections. Antibiotics and antibiotic/steroid combinations were the most common category of interacting drugs. When prescribing new medications, ideally a non-interacting drug should be chosen. Where this is not possible, more frequent INR monitoring and dose alteration is necessary until the course of medication is completed or warfarin control has stabilised. This is routinely encouraged in the warfarin clinic.

Prescription and pre-analytical errors resulting in an elevated INR are amenable to reduction in the future. A typical example of a prescription error included clerical errors in dosage charts in patients resulting in overdosing, although some cases involved unexplained dosage increase by medical staff with the INR within therapeutic range. Three cases of minor haemorrhage were associated with prescription errors. Pre-analytical errors primarily involved
inappropriate methods of specimen collection. An example of these errors would include a specimen taken from a patient intravenous line resulting in dilution of patient plasma giving a falsely elevated INR. No episodes of haemorrhage were reported with these types of errors.

Initiating warfarin therapy is undoubtedly one of the most difficult aspects of warfarin management. As well as the frequent elderly age of the patient, the physician may encounter a previously unknown bleeding risk, sensitivity, or resistance to oral anticoagulant effects. One common pitfall is the unnecessary urgency to achieve a therapeutic INR for chronic indications, e.g. atrial fibrillation. A previous audit of the start of anticoagulant treatment reported that 58% of INR results were not therapeutic upon patient discharge.

Most hospitals or surgeries initiate warfarin with high loading doses, most often ten milligrams on days one and two of therapy. This audit discovered 30 cases (9.9%) of INR=5.0 with 1 associated minor haemorrhage event due to overdose at induction, thereby confirming this as a significant cause of over-anticoagulation. Multiple studies have confirmed the fallacy of relying on a high loading dose, which can potentially result in early over-anticoagulation and the development of a potential hypercoagulable state. It has been demonstrated that a 10-mg loading dose is unlikely to be more effective than a 5-mg dose in achieving a therapeutic INR by day 4 or 5 of therapy.

The annual incidence of major (1.3%) and minor (15.3%) haemorrhages per INR ≥5.0 episode appears to be broadly in line (allowing for differences in definition) with large clinic population studies showing major haemorrhage rates of 2% and minor haemorrhage rates of just over 5%. Comparison is difficult because the criteria for defining the severity of bleeding vary considerably between studies, accounting in part for the variation in the rates of bleeding. We acknowledge the limitations in using INR=5.0 in calculating the incidence of haemorrhages, including the fact that patients experiencing haemorrhage within INR range or less than 5.0 were not systematically identified. In addition, most intracranial haemorrhages occur with INR within therapeutic range. However, during the audit period, no fatal or intracranial haemorrhage in warfarinised patients (with any INR range) was reported. Of the 932 patients attending the MWRH clinic in the 12-month audit period, only one experienced a thromboembolic event. This patient was within INR therapeutic range at the time of the embolus being diagnosed.

There is a continuous need to monitor the standards of anticoagulation achieved and the quality of service delivered. The age standardised rates in this study allow more detailed service delivery planning which clearly needs to be targeted to the needs of the elderly population. The information in this audit may be useful to other HSE areas within Ireland to assist with benchmarking and service planning.

**References**


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