



Brief Communication

# Anticoagulation clinics for children achieve improved warfarin management

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## Introduction

Oral anticoagulant therapy is difficult to manage in children as the children who require anticoagulation usually have complex underlying health problems, are on multiple medications and are often difficult to venesect. Multiple studies in adults have demonstrated that dedicated anticoagulation clinics (AC) achieve superior results in terms of keeping patients within their specified target therapeutic range (TTR). One of the most important advantages of AC management of warfarinised patients is the provision of regular, consistent education and feedback to the patient by the same staff members [2–8]. There is only one previous report of a paediatric AC. In 1999, we established a nurse-coordinated paediatric AC with emphasis on parent education, whole tablet dosing and monitoring protocols. This report is the first analysis of this program.

Significant paediatric medical advances in the last decade have seen patients for whom no therapy was known 10 years ago, now receiving life saving care. This reduction in infant and child mortality is not without sequelae, however, and thromboembol-

ic disease is now recognised as a potential adverse event for many children presenting with serious health problems. This increased risk of thromboembolic disease has significantly contributed to the increased use of warfarin in paediatrics, both therapeutically and prophylactically [9].

Despite the advances that have been made in the management of seriously ill children, the delivery of effective warfarin therapy to infants and children remains a challenge. Streif et al, in the largest published cohort of children requiring warfarin therapy, achieved the target therapeutic range (TTR) INR in only 54% of test points. Warfarin use in children has proven to be a greater challenge than warfarin use in adults. Reasons include variable age-related dose response rates, frequent concomitant medications, chronic health conditions and frequent intercurrent illnesses [9–14]. Lack of control over these confounding factors can contribute to an increase in warfarin related adverse events [15]. Strategies that minimise the impact of these confounding variables are needed to optimise anticoagulant management in infants and children. Such strategies are most likely to be generated through a dedicated paediatric AC.

## Methods

In 1999 a dedicated paediatric AC was established at the Royal Children's Hospital, Melbourne, Australia.

**Abbreviations:** INR, international normalised ratio; TTR, target therapeutic range; AC, anticoagulation clinic; DVT, deep vein thrombosis; CVAD, central venous access device; TPN, total parenteral nutrition.

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This clinic comprised Consultant Haematologists and an Anticoagulation Nurse, and incorporated the services of the hospital's Pathology Collection department and Core Laboratory. The Anticoagulation Nurse made all clinical management decisions, supervised by a Consultant Haematologist.

A prospective audit of results for the third year of this program (Dec 2001–Nov 2002) was conducted. All patients received warfarin therapy (*Coumadin* or *Marevan*, Boots Healthcare Australia, North Ryde NSW, Australia). All dosing decisions incorporated the use of whole tablet doses, with alternate night dosing regimens being preferred to breaking tablets. Dosing nomograms were not used in any patients. All dose adjustments were made according to individualised dosing regimes, taking into account the INR result, the presence of confounding factors and the patient's known anticoagulant history.

All patients were reviewed in the AC on at least an annual basis.

Anticoagulant therapy was monitored using the Prothrombin time, reported as an international normalised ratio (INR). Standard of care monitoring during the period of study was the CoaguChek™ S Point of Care monitor (Roche Diagnostics, Castle Hill, NSW, Australia).

Data collection included basic demographics, in-/outpatient status, INR results defined as within or outside TTR, reasons for non-achievement of TTR, major bleeding and thrombotic complications. All patients had a target INR, however, for ease of reporting, all INR results were reported as within or outside of the TTR. Warfarin dose adjustments were not limited to patients recording an INR outside of the TTR, but may have been implemented if the INR did not meet the desired target.

Children classified as having a cardiac indication for anticoagulant therapy included those with prosthetic valves, pulmonary hypertension, cardiomyopathy, post Fontan surgery or another cardiac anomaly.

One child with homozygous protein C deficiency was excluded from analysis. He had a target therapeutic

range of 4.0–5.0. Exclusion was based upon difficulty in determining the incidence of bleeding and thrombotic events in this patient, as well as the disproportionate number of INRs performed and the overwhelming disease-specific problems with warfarin therapy.

For the purpose of analysis, a *p*-value of less than 0.05 was considered to be statistically significant.

## Results

Ninety-four children received warfarin for a total of 61.8 warfarin years (range: 1 week to 12 months). The children ranged in age from 3 months to 20 years. There were 50 females and 44 males. The majority of patients had an underlying cardiac anomaly, consisting of Fontan patients (*n*=30), prosthetic valves (*n*=11), cardiomyopathy (*n*=11), pulmonary hypertension (*n*=9) and other forms of congenital heart disease (*n*=6). Fifteen patients with short gut anomalies received concomitant warfarin therapy. These children were divided into two groups: those that had objective radiological imaging confirming venous thrombosis and those that had never been diagnosed with a thrombosis. The majority of patients receiving warfarin had significant underlying health problems.

The TTR was achieved 63.4% of INR tests. INRs were supra-therapeutic 11.7% and sub-therapeutic 24.9% of the time. Table 1 presents TTR achievement by age group, with mean frequency of INR tests required per month in each group. Less-than-1-year-olds are clearly therapeutic less often than older children (*p*<0.0008). Patients requiring warfarin therapy for the treatment of thromboembolic disease achieved their TTR 69.1% of tests compared to children receiving prophylactic anticoagulation 62.2% (*p*=0.08).

Table 2 presents a breakdown of TTR achievement by clinical indication for anticoagulant therapy. 63.6% of all warfarinised patients had an underlying cardiac anomaly. Patients not within their TTR were more likely to be subtherapeutic

**Table 1** Target therapeutic range achievement and frequency of monitoring tests related to age

| Age (years) | Number of children | Mean number of tests/month | Percent in TTR | Percent high  | Percent low    |
|-------------|--------------------|----------------------------|----------------|---------------|----------------|
| ≤1          | 7                  | 6.8                        | 49.2 (60/122)  | 14.8 (18/122) | 36.0 (44/122)  |
| >1–5        | 13                 | 3.9                        | 61.5 (209/340) | 10.9 (37/340) | 27.6 (94/340)  |
| >5–10       | 23                 | 2.6                        | 66.9 (333/498) | 10.8 (54/498) | 22.3 (111/498) |
| >10–15      | 24                 | 2.6                        | 65.7 (305/464) | 10.1 (47/464) | 24.2 (112/464) |
| >15         | 27                 | 1.8                        | 62.4 (302/484) | 14.0 (68/484) | 23.6 (114/484) |

**Table 2** Target therapeutic range achievement related to indication for warfarin

| Indication for warfarin | Number of patients | Number of tests | Percent of time in TTR | Of total number of INRs |                     |
|-------------------------|--------------------|-----------------|------------------------|-------------------------|---------------------|
|                         |                    |                 |                        | Percent of time high    | Percent of time low |
| Cardiac                 | 67                 | 1214            | 64.3                   | 11.9                    | 23.8                |
| CVAD prophylaxis        | 6                  | 56              | 92.9                   | 5.3                     | 1.8                 |
| CVAD related thrombosis | 9                  | 444             | 55.2                   | 12.4                    | 32.4                |
| Ischaemic stroke        | 3                  | 35              | 68.6                   | 5.7                     | 25.7                |
| Arterial thrombosis     | 2                  | 71              | 69                     | 14.1                    | 16.9                |
| Other DVT               | 7                  | 88              | 67                     | 10.3                    | 22.7                |

rather than supratherapeutic, except for children requiring warfarin for central venous access device (CVAD) prophylaxis.

At the time of testing, 73.4% of children were outpatients. There was no statistical difference in TTR achievement between inpatients (65.5%) and outpatients (62.6%).

Causes for being non-therapeutic were identified in 39.3% of cases, commonly medication changes (19%) and deterioration in health status (17.5%). Dietary change was only identified as a contributing factor in 3.7% of cases. Patients older than 15 years were more likely to be non-therapeutic due to omitted doses than any other age group.

There was one episode of major bleeding during the period of study. One adolescent girl had menorrhagia requiring admission to hospital (INR 2.8), but did not require transfusion. Two children had thrombosis on treatment [intracardiac/embolic stroke INR 2.0; prosthetic tricuspid valve INR 2.3]. The combined major bleeding and thrombotic complication rate was 1.86 events/patient year.

All-cause mortality was 6.9%. There was one direct thrombosis-related death. The child who developed an intracardiac thrombosis in the setting of deteriorating cardiomyopathy (INR 2.0) had an embolic stroke and treatment was subsequently withdrawn.

## Discussion

This prospective study evaluated the efficacy and safety of a specialised paediatric AC. All patients requiring warfarin over a 12-month period were included in this study, except the child with homozygous protein C deficiency. Primary indications for oral anticoagulant therapy likely reflect institutional specialisation and local medical management strategies. Warfarin use in children is primarily prophylactic, with few children in our series re-

quiring warfarin for the management of confirmed venous or arterial thromboses. This study demonstrates a greater rate of target therapeutic range achievement in children than has previously been published [9,11]. Comparisons of major bleeding events are hampered by lack of definition in comparative papers, but appear to be reduced in the current series [9,11].

In 1994, Andrew reported that 49% of anticoagulated children from the Hospital for Sick Children had an underlying cardiac anomaly [11]. The representation of cardiac anomalies in warfarinised patients at the same institution increased to 51% in the follow-up series reported by Streif in 1999 [9]. The Royal Children's Hospital, Melbourne is the major paediatric cardiac surgical unit in Australia, which may reflect the even higher representation of cardiac disorders (63.6%) necessitating warfarin therapy in the current series. Advances in both the medical and surgical management of congenital heart disease have significantly contributed to the current context of warfarin management, which differs significantly from that seen in adults [8]. In 1992, Evans et al. [16] found that the major indication for oral anticoagulant therapy in children was prophylaxis of prosthetic heart valves. Although such children remain a significant subpopulation of an anticoagulant clinic, they represent only 11% of the total population of children described in this series. The single most frequent indication for warfarin therapy in the current series was thromboprophylaxis following Fontan surgery, comprising 32% of children. Conditions such as hypoplastic heart syndrome and tricuspid atresia have been successfully palliated with the Fontan procedure, achieving improved long-term outcomes [17]. Children post Fontan surgery receive routine warfarin prophylaxis for life at RCH, hence their large contribution to this series. Children requiring long-term total parenteral nutrition (TPN) via CVADs have been reported to be at significant risk of catheter-related thromboses [1,18–21]. Of the patients in the Andrew and Streif

series, 5% and 2.5%, respectively, had a requirement for long-term TPN as their primary indication for oral anticoagulant therapy [9,11]. In the current series, 16% of children reported were receiving warfarin for either the management or prevention of catheter-related thrombosis in the setting of long-term TPN. Only 12.5% of INR tests performed during the period of study were related to the management of an acute thrombotic event in either the arterial or venous system. No patient in this series had an underlying malignancy or systemic lupus erythematosus.

Achievement of the TTR in patients requiring warfarin for the treatment of a thromboembolic event was greater (69.7%) than that seen in patients requiring prophylactic warfarin therapy (62.7%). This may reflect a less aggressive approach to achieving TTR in patients who have never had a thrombotic event, as evidenced by the increased likelihood of patients not achieving the TTR to be subtherapeutic. Children requiring warfarin for the management of catheter-related thromboses achieved their TTR less frequently than any other sub-population of children (55.2%). Non-achievement of the TTR in this sub-population was frequently associated with changes in medications (29%) and deterioration in health status (13%). For children receiving parenteral nutrition, Vitamin K was not removed from the parental solution. We have previously published a study demonstrating the ability to adequately anticoagulate children despite routine Vitamin K supplements in TPN [1].

Children less than 1 year of age represent a significant challenge to an anticoagulation service. As with the majority of children in this cohort, they are likely to have significant underlying health problems that require multiple concomitant medications, frequently develop intercurrent illnesses and are difficult to bleed for monitoring tests. These confounders to stable therapy are further compounded by the dietary challenges associated with breast versus bottle-feeding and the introduction of solid foods. These dietary issues complicate the achievement of stable therapy as they significantly impact upon Vitamin K intake, making determination of warfarin doses very difficult. Children less than 1 year of age achieved their TTR at 49.2% of test points, compared to 64.3% in the remainder of children in this series ( $p < 0.0008$ ). We confirm a previous report, in which TTR was achieved in 37% of this age group, identifying less-than-1-year-olds as the most difficult group to keep within the therapeutic window [9]. Children less than 1 year of age had monitoring tests performed with greater frequency than older children, with

the interval between tests increasing with advancing age.

No thrombotic events on warfarin were reported in either of the series from the Hospital for Sick Children [9,11]. The two patients who developed thrombotic events on treatment in this series were within or just under their TTR. Diminished flow was likely to be a significant contributing factor in the child who developed an intracardiac thrombosis in the setting of progressive cardiomyopathy. There were no other contributing factors identified in the child who developed a tricuspid valve thrombosis with an INR of 2.3. This patient's TTR was subsequently increased to 3.0–4.5 in combination with aspirin, and she has had no further thrombotic events. Major bleeding was not defined in either the Andrew or Streif papers, making comparison of major bleeding event rates difficult. The four major events reported in both papers comprised two intracranial haemorrhages and two patients requiring blood transfusion [9,11]. The one major bleeding event in the current series did not require transfusion and was classified as major on the basis of the need to admit the child to hospital for observation. While there is debate about the classification of bleeding, our study conforms to the ACCP guidelines [22]. Even using the broadest available definition of major bleeding, we had only one event in 61.8 warfarin years across all TTRs (0.66 events/patient year). Significant bleeding is reported previously at a rate of 1.7 events/patient year in all children, with children with prosthetic heart valves having an incidence of  $< 3.2$  events/patient year [10]. The all-cause mortality in this series (6.9%) reflects with significant underlying health problems existing in this cohort of children.

In summary, experience with oral anticoagulation amongst general and many sub specialist paediatricians is limited. For a number of physiological and pathological reasons, infants and children are generally accepted as being more difficult to maintain in the TTR. Our study has shown improved results compared to previous published paediatric data, and results comparable to some adult studies. A defined nurse-coordinated paediatric AC with appropriate backup and support is a worthwhile model for the support of children requiring anticoagulation therapy.

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