ABSTRACT. Objective. To determine whether warfarin can be safely administered to children who require long-term total parenteral nutrition (TPN), for the purpose of preventing central venous access device (CVAD)-related thrombosis.

Methods. A prospective cohort study was conducted of 8 children with short-gut syndrome or small intestinal anomalies. All patients received oral anticoagulant therapy (warfarin) managed by the hematology department at a tertiary pediatric center. Data collected included demographic details, nutritional intake, age, weight, history of deep vein thrombosis, number and functional duration of CVADs, warfarin requirements, and adverse event rates.

Results. A total of 15.2 warfarin years were studied prospectively. The target therapeutic range was achieved 51.1% of time. The mean dose of warfarin required to achieve the target therapeutic range (international normalized ratio) of 2.0 to 3.0 was 0.33 mg/kg/d. The mean duration between warfarin monitoring tests was 6.6 days. The median vitamin K intake per patient was 0.367 mg/kg/d (range: 0.018–2.85 mg/kg/d). Before commencing anticoagulant therapy, the mean CVAD duration was 160.9 days. Concomitant warfarin therapy was associated with a mean CVAD duration of 351.7 days. There were no major bleeding events, and no clinical extension of thrombosis was observed.

Conclusions. This is the first published study to report uniform warfarin prophylaxis for CVADs in children. Warfarin therapy can be administered safely in children who require long-term TPN. Warfarin prophylaxis seems to prolong CVAD survival. Pediatrics 2003;112:e386–e388. URL: http://www.pediatrics.org/cgi/content/full/112/5/e386; total parenteral nutrition, warfarin, central venous access device, short-gut syndrome.

ABBREVIATIONS. TPN, total parenteral nutrition; CVAD, central venous access device; TTR, target therapeutic range; INR, international normalized ratio.

Warfarin therapy in children and infants is complicated by many factors. These include age-related dose-response variation, concomitant medications, monitoring challenges, multiple underlying medical disorders, method of administration of warfarin, and dietary changes.1–4 Children who have short-gut syndrome and are on long-term total parenteral nutrition (TPN) present an additional challenge to effective anticoagulant therapy. Warfarin therapy may be indicated in this population because of their dependence on central venous access for TPN. Central venous access devices (CVADs) are the single most frequent predisposing factor for venous thromboembolic disease in infancy and childhood.5–7 CVAD-related thrombosis is common in patients who require long-term TPN, resulting in the placement of multiple CVADs over time.8 The use of low-dose warfarin to prevent CVAD-related thrombosis has been reported in the adult literature, but no studies have reported routine anticoagulant prophylaxis using warfarin in children. We present a cohort of 8 TPN-dependent children, aged between 6 months and 16 years. All receive warfarin therapy for prophylaxis and/or treatment of CVAD-related thrombosis.

METHODS

A prospective cohort study was conducted of children (N = 8) who have short-gut syndrome or small intestinal anomalies and require long-term TPN in whom warfarin therapy was managed by the hematology service at a tertiary pediatric hospital. Primary outcomes assessed were achievement of target therapeutic range (TTR), warfarin dose requirements, CVAD patency, and warfarin-related adverse events. Other data collected included patient demographics, vitamin K intake, frequency of international normalized ratio (INR) monitoring, CVAD, and thrombosis history.

The protocol was that warfarin was commenced at a dose of 0.3 mg/kg/d (rounded to the nearest whole tablet) and titrated to achieve a TTR (INR) of 2.0 to 3.0 in children with existing thrombosis and 1.3 to 2.0 in children without. Vitamin K was not removed from parenteral nutrition.

A Medline literature search, search via OVID, was performed using the following key words: “warfarin,” “children,” “short gut syndrome,” “short bowel syndrome,” “central venous access device,” “venous thrombosis,” and “total parenteral nutrition.”

RESULTS

Table summarizes the demographic details of the patient population according to underlying small intestinal pathology (including surgical resections), history of thrombosis, and age. All children had a minimum of 4 nights per week of TPN administered via a CVAD, receiving Synthamin parenteral nutrient solution. Seven of the 8 children in this series (all <11 years of age) received 0.2 mg of vitamin K per day via that solution. The 16-year-old received 2 mg vitamin K/L of nutrient solution, equating to approximately 3 mg of vitamin K per day. Total daily vitamin K intake is presented in Table 1.
A total of 15.2 warfarin years were observed in this population. Mean duration of therapy was 691.6 days (median: 817 days; range: 186-1025 days). The mean interval between INR test points was 6.6 days. All INR tests were performed within the 1 tertiary center’s pathology department. Samples were collected either via fingerprick (CoaguchekS; Roche Diagnostics, Sydney, Australia) or from a CVAD (buffered 3.2% citrate tube, Stago Compact; Diagnostica Stago, Asnieres, France). The TTR was achieved in 51.1% of test points across the entire population (median: 54.75%). The median achievement of TTR was 69.4% in patients with a TTR of 1.3 to 2.0 and 51.9% in patients with a TTR of 2.0 to 3.0. The mean dose of warfarin required to achieve a TTR of 2.0 to 3.0 was 0.33 mg/kg/d (range: 0.125–0.65). The mean dose of warfarin required to achieve a TTR of 1.3 to 2.0 was 0.26 mg/kg/d (range: 0.16–0.37). There was no correlation between warfarin dose (mg/kg/d) and vitamin K intake (mg/kg/d; $r^2 = 0.1193$). There were no major bleeding events during this study period. Individual warfarin requirements are summarized in Table 1.

On referral to the hematology unit, 6 of the patients had existing venous thrombosis associated with CVADs. This was confirmed by radiologic imaging techniques including ultrasound for the femoral, iliac, and jugular veins and the lower inferior vena cava; venography for central veins within the thoracic cage; and magnetic resonance venography. Patients were not routinely reimaged. No clinical signs of thrombosis recurrence or new thrombotic complications were observed during this period of study.

A total of 6682 CVAD days with warfarin therapy were followed, and the average CVAD duration was 351.7 days. This was compared with historical data on the same patient population, which showed that for 5543 CVADs before warfarin therapy, the average CVAD duration was 160.9 days. When a CVAD was in situ at the time of commencing warfarin, that catheter’s duration was “split” between both arms of the analysis.

**DISCUSSION**

Infants and children with short-gut syndrome and small intestinal anomalies can be sustained on TPN long term without compromising their developmental milestones. However, these children represent a significant challenge because of their dependence on central venous access for survival. In a large multicenter registry study, CVADs were associated with >60% of venous thrombosis in children. CVADs predispose to thrombus formation as a result of injury to the vessel wall, disruption of blood flow, and the infusion of irritant fluids. Loss of vascular access as a result of chronic thrombosis is life-threatening for these patients. Previous studies suggested that warfarin prophylaxis in adult patients who require long-term central venous access is associated with improved catheter-related outcomes. The safety and efficacy of warfarin therapy in children with such pathology has not been previously examined.

The cohort of children who are dependent on TPN
represents all that is difficult in delivering effective anticoagulant therapy to children. Concomitant warfarin therapy may produce improved catheter-related outcomes but, if not adequately controlled, could produce new adverse events, including major bleeding.

This small study demonstrated that warfarin can be delivered safely to children who are on long-term TPN. There were no major bleeding events and no incidents of clinically apparent thrombosis. The achievement of the TTR in 51.1% of test points is not discordant with current rates of TTR achievement in general pediatric populations. One adolescent patient within this cohort who had compliance issues significantly skewed this mean TTR achievement, reaching her TTR at only 32% of test points.

The need for vigilant monitoring of this cohort is clear, with INR monitoring tests being performed every 6.6 days. This figure reflects the number of hospital admissions experienced by this cohort, during which time warfarin therapy was monitored more frequently. As outpatients, it was rarely possible to extend the frequency of INR monitoring beyond 2 weekly. The need for frequent INRs illustrates that although these patients can be treated safely on warfarin, they need a high level of supervision and as such may best be treated by a dedicated thrombosis service.

Contradictory information exists as to the likelihood of warfarin resistance in this population, as a result of both their vitamin K intake and their underlying gut pathology. In the past, it has been suggested that vitamin K should be removed from parenteral nutrition for children who require warfarin therapy. Other authors have suggested that warfarin resistance occurs in patients with short-gut pathologies, irrespective of vitamin K content of TPN. In this study, vitamin K was not removed from the parenteral solutions. When viewed in context with age-adjusted warfarin requirements (0.09 [±0.01] to 0.32 [± 0.05] mg/kg/d), our patients did not demonstrate warfarin resistance.

Our study is the first to report routine warfarin prophylaxis for children with long-term CVADs, and this prospective study suggests that warfarin therapy can be administered safely and effectively to children with small intestinal anomalies requiring long-term TPN. There seemed to be an improvement in catheter-related outcomes, as evidenced by a significant prolongation of catheter duration; however, additional study is needed to confirm this finding. Patients with small intestinal anomalies requiring TPN present a significant challenge to a thrombosis service but can be treated with warfarin without the removal of vitamin K from their parenteral and enteral formulas and without significant risk of bleeding.

REFERENCES
Warfarin Therapy in Children Who Require Long-Term Total Parenteral Nutrition
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