Congenital heart disease, with a wide spectrum of severity, affects approximately 1% of all live births. The majority of congenital cardiac structural abnormalities occur in otherwise healthy children and total correction of the cardiac lesion usually results in a normal productive lifespan. Thromboembolic disease has been termed the new epidemic of paediatric tertiary care hospitals. Nowhere is this more evident than in cardiac and cardiac surgical patients. Improved survival for these patients over the last decade has been the result of tremendous advances in surgical techniques, availability of new drugs and new applications for old drugs, and developments in critical and supportive care. Despite this, one of the most frequent complications seen in survivors of congenital heart disease is thromboembolism, which include venous, arterial, and intracardiac thrombosis, pulmonary embolus, and embolism to the central nervous system (CNS) (fig 1). Venous thromboembolic disease in children with congenital heart disease has a mortality of approximately 7%. Morbidity in the form of post-phlebitic syndrome (fig 2) and recurrent venous thrombosis occurs in over 20% of children.

Infants and children with congenital heart disease constitute a major proportion of paediatric patients seen in tertiary hospitals with thromboembolism. Recent data show that almost 50% of infants less than 6 months old, and 30% of older children who suffer venous thromboembolic disease have underlying cardiac disorders. Similarly, almost 70% of infants (< 6 months) and 30% of children who suffer arterial thromboembolism have underlying cardiac defects. In addition, the majority of children on primary anticoagulant prophylaxis are being treated for complex congenital heart disease or severe acquired cardiac illness.

Thus physicians and surgeons who care for paediatric patients with congenital heart disease commonly use anticoagulation treatment.1 There are a multitude of important variables which make the use of anticoagulant drugs in paediatric patients different from the use of the same drugs in adults. This article will discuss many of these issues, and their implications. Finally, the current data about adverse effects associated with anticoagulant use in paediatric patients will be presented.

VARIABLES AFFECTING USE OF ANTICOAGULANT DRUGS IN PAEDIATRICS

Epidemiology of thromboembolic disease in paediatric patients

The epidemiology of thrombosis in paediatric patients was poorly understood until recently. Over the last 10 years there have been a number of national and international registries published for both neonates and children.2–7 While there are some conflicting data, there is uniformity about the high proportion of secondary thrombosis in children with major underlying disease, the overwhelming role of central venous access devices in the aetiology of thrombosis (fig 3), and the biphasic age dependence with neonates and adolescents being at highest risk for thrombosis. This last fact probably reflects, in part, the age distribution of major illnesses which require central venous access such as congenital heart disease and cancer, but also the influence of small physical size of blood vessels related to central venous access devices in neonates and the maturation of the coagulation system in adolescents. The epidemiological differences between adults and paediatric patients with thromboembolism almost certainly alter the risk:benefit ratio of anticoagulation treatment.

Developmental haemostasis

The haemostatic system is a dynamic evolving entity, which not only likely affects the frequency and natural history of thromboembolic disease in children, but also the response to therapeutic agents.8–12 The concept of developmental haemostasis was first coined in the late 1980s and is now uniformly accepted. Not only are the plasma values of many individual coagulation proteins different in paediatric patients from adults, but the global functioning of the coagulation system appears to be quite different. In addition to quantitative differences, there is evidence (mostly from animal models) of qualitative differences in many coagulation proteins, especially in neonates.13 14 Finally, again from animal models, data would support significant differences in the
antithrombotic properties of the blood vessel wall, with altered concentrations of active glycosaminoglycans.\textsuperscript{15} The differences in plasma proteins most likely to have an impact on anticoagulation treatment are as follows, although ongoing research in this area is desperately needed. Plasma concentrations of antithrombin (AT) are physiologically low at birth (approximately 0.50 U/ml) and do not increase to adult values until three months of age. Sick premature neonates frequently have plasma concentrations of AT of $<0.30$ U/ml. Fetal reference ranges are now available and show that AT values range from 0.20–0.37 U/ml at gestational ages of 19–38 weeks. This likely has a profound effect on the action of heparin, the antithrombotic activity of which is dependent on catalysis of AT to inactivate specific coagulation enzymes, in particular thrombin. The capacity of plasmas from neonates to generate thrombin is both delayed and decreased compared to adults, and similar to plasma from adults receiving therapeutic amounts of heparin.\textsuperscript{16} Following infancy, the capacity of plasmas to generate thrombin increases but remains approximately 25% less than for adults throughout childhood.\textsuperscript{17} Both an increased sensitivity and resistance to unfractionated heparin's anticoagulant activities have been reported in vitro in plasma from neonates. Increased sensitivity to unfractionated heparin is observed in systems based on assays dependent on thrombin generation (for example, activated partial thromboplastin time (APTT)). The in vitro effects of unfractionated heparin (0.25 U/ml) on neonates, children, and adults were compared recently, and thrombin generation was delayed and reduced in children compared to adults, and virtually absent in neonates.\textsuperscript{14} Resistance to unfractionated heparin is observed in systems based on assays that measure the inhibition of exogenously added factor Xa or thrombin and that are dependent on plasma concentrations of AT.

Similarly, in vitro, thrombin generation is similar in adults and children at the same concentration of low molecular weight heparin (LMWH); however, at 0.25 U/ml LMWH, thrombin generation was delayed and reduced by approximately half in newborns compared to adults. These differences were matched by reductions in rates of prothrombin consumption.\textsuperscript{19}

The vitamin K dependent factors are the most extensively studied group of factors in infants. Physiologically low concentrations of factors (F)II, FVII, FIX, and FX were measured in infants who received vitamin K prophylaxis at birth. The concentrations of the VK dependent factors and the contact factors (FXI, FXII, prekallikrein, and high molecular weight kininogen) gradually increase to values approaching adult levels by 6 months of life. For children receiving vitamin K antagonists, the capacity of their plasmas to generate thrombin is delayed and decreased by 25% compared to plasmas from adults with similar international normalised ratios (INRs).\textsuperscript{19}

Whether the overall activity of the protein C/protein S system varies with age is unknown. However, at birth,
plasma concentrations of protein C are very low, and they remain decreased during the first six months of life. Although total amounts of protein S are decreased at birth, functional activity is similar to that in the adult because protein S is completely present in the free, active form due to the absence of C4 binding protein. Furthermore, the interaction of protein S with activated protein C in newborn plasma may be regulated by the increased concentrations of 2 moi-
globulin. Plasma concentrations of thrombomodulin are increased in early childhood, decreasing to adult values by late teenage years; however, the influence of age on endothelial cell expression of thrombomodulin has not been determined. Total tissue factor pathway inhibitor (TFPI) concentrations in newborns are reported as being similar to those in older children or adults. Free TFPI is reported as being significantly lower in newborns.

Distribution, binding, and clearance of antithrombotic drugs
The distribution, binding, and clearance of antithrombotic drugs are age dependent. Studies of unfractionated heparin in newborns are limited but show that the clearance is faster than for older children because of a larger volume of distribution, and that the dose of unfractionated heparin required to achieve a therapeutic APTT is also increased compared to older children. Pharmacokinetic studies in piglets also show that the clearance of unfractionated heparin is faster than for adult pigs because of a larger volume of distribution. Heparin binding may also be different, although this remains to be proven. These factors presumably cause the noted age related differences in heparin dosing. Bolus doses of 75–100 U/kg result in therapeutic APTT values in 90% of children (unpublished data). Maintenance heparin doses are age dependent, with infants (up to 2 months corrected for gestational age) having the highest require-
ments (average 28 U/kg/hour) and children over 1 year of age having lower requirements (average 22 U/kg/hour). The doses of heparin required for older children are similar to the weight adjusted requirements in adults (18 U/kg/hour).

The doses for LMWH are also age dependent, and exhibit far more patient to patient variability in neonates and children, than seen in adults. In general, peak anti-factor Xa values occur 2–6 hours following a subcutaneous LMWH injection. Infants less than approximately 2–3 months of age or less than 5 kg have increased requirements per kg likely due to a larger volume of distribution. Alternative explanations for the increased requirement of LMWH per body weight in young children include altered heparin pharmacokinetics and/or a decreased expression of anticoagulant activity of heparin in children caused by decreased plasma concentrations of AT.

For warfarin, the published age specific, weight adjusted doses for children vary because of the different study designs, patient populations, and possibly the small number of children studied. The largest cohort study (n = 263) found infants required an average of 0.33 mg/kg and teenagers 0.09 mg/kg warfarin to maintain a target INR of 2–3. For adults, weight adjusted doses for vitamin K antagonists are not precisely known but are in the range of 0.04–0.08 mg/kg for an INR of 2–3. The mechanisms responsible for the age dependency of vitamin K antagonist doses are not completely clear.

Drug formulations
There are no specific paediatric formulations of antithrombotic drugs, making accurate, reproducible weight adjusted dosing difficult. This is especially the case for vitamin K antagonists (no suspension/liquid preparation). Although the tablets can be dissolved in water for administration to newborns, there is no stability data or critical assessment of this practice. LMWHs are available most readily in pre-dosed syringes. Thus LMWHs are considerably more complex for parents to learn how to administer at home to their children, as often they must draw up smaller individual doses from prefilled syringes.

In most countries, all anticoagulant drugs remain unlicensed in children, requiring “off label” use, as the studies required to get formal approval have never been completed.

Dietary differences
Dietary differences, especially in infants, where breast milk and infant formulas have vastly different vitamin K concentrations, makes oral anticoagulation particularly difficult. Infant formula is supplemented with vitamin K to prevent haemorrhagic disease of the newborn which makes formula fed infants resistant to vitamin K antagonists. Formula fed infants may require high doses of warfarin to achieve therapeutic INRs, sometimes as much as 15 mg/day. This substantially increases the risk of bleeding, should the infant have an intercurrent illness and reduce their formula intake transiently. In contrast, breast milk has low concentrations of vitamin K, making breast fed infants very sensitive to vitamin K antagonists. The latter can be compensated for by feeding breast fed neonates 30–60 ml/kg of formulae each day.

Other patient related differences
The need for general anaesthesia to perform many diagnostic studies in paediatric patients impacts on the ability to confirm and monitor thromboembolic disease and hence the certainty of therapeutic decisions. Vascular access, while a major cause of thromboembolism in paediatric patients, also presents significant difficulties in treating thromboem-

bolic disease. Frequently, the choice of antithrombotic agent is decided by the practical ability to deliver the drug. Often, the only vascular access available is used for drug delivery, and so accurately monitoring blood anticoagulant values is not possible. With respect to oral anticoagulation, the frequency and type of intercurrent illnesses and concurrent medications varies with age. In particular, small infants have frequent viral infections, which often makes warfarin management more difficult. Finally, compliance issues are vastly different in, for example, small infants who cannot understand the need for treatment, adolescents who intellec-
tually comprehend but emotionally are unable to cooperate, and children in dysfunctional families who suffer the effects of inadequate parenting. The social, ethical, and legal implications of these issues frequently interfere with the ability to provide the “best” “treatment for individual infants and children and cannot be underestimated.

Lack of quality evidence for treatment guidelines
Recommendations for antithrombotic treatment in paediatrics have been extrapolated from recommendations for adults because thromboembolic events in paediatrics were previously rare enough to hinder testing of specific therapeutic modalities, yet common enough to present
significant management dilemmas that required therapeutic intervention.

The most widely used guidelines for anticoagulation treatment in neonates and children are the American College of Chest Physicians (ACCP) consensus conference guidelines. Since the first publication of paediatric guidelines in the 1995 Chest antithrombotic supplement, less than 10 multinational randomised controlled intervention trials assessing specific aspects of anticoagulant treatment in children have been initiated and most of these have failed to enrol adequate patients to answer the primary study question. This is a stark contrast to the number of trials completed to determine optimal anticoagulant treatment for adult patients. The majority of literature available to support the paediatric recommendations are uncontrolled studies, case reports or in vitro experiments.

In this context, the use of anticoagulant treatment in children remains based on uncertainty and often unsubstantiated opinion.

ADVERSE EFFECTS OF ANTICOAGULATION IN PAEDIATRICS

Haemorrhagic complications

The most important adverse effect of any anticoagulant drug is bleeding. Many of the same factors which affect other aspects of anticoagulant use, also likely affect the risk of major bleeding.

One cohort study reported bleeding in 1.9% (95% confidence interval (CI) 0.1% to 10.2%) of children treated with heparin for deep venous thrombosis or pulmonary embolus. However, many children were treated with suboptimal amounts of heparin (compared to target APTT) in this study and further studies are required to determine the true frequency of heparin induced bleeding in children.

There are few studies reporting bleeding risk for LMWHs. One pilot study reported no bleeding documented in seven infants less than 2 months of age (0%, 95% CI 0% to 47%).

In a larger series, 4 of 37 infants had major bleeding (10.8%, 95% CI 3% to 25.4%). The locations were local at the site of subcutaneous catheters in two newborns with little subcutaneous tissue and into pre-existing abnormalities in the CNS in a further two newborns. In children, a single institution cohort study of 146 courses of therapeutic enoxaparine, major bleeds occurred in 4.8% (95% CI 2% to 9.6%) of patients. In a randomised trial (n = 37) of reviparin, major bleeding occurred in 8.1% (95% CI 1.7% to 21.9%).

The risk of serious bleeding in children receiving vitamin K antagonists for mechanical prosthetic valves is less than 3.2% per patient year (13 case series). In one large cohort (391 warfarin years, variable target range) bleeding rate was 0.5% per patient year. In a randomised trial (n = 41) with a target range 2–3 for three months, bleeding occurred in 12.2% (95% CI 4.1% to 26.2%).

Non-haemorrhagic complications

Heparin and LMWH

There are only three case reports of paediatric heparin induced osteoporosis, two of which received concurrent steroid treatment. The third received high dose intravenous heparin treatment for a prolonged period. However, given the convincing relation between heparin and osteoporosis in adults, long term use of heparin in children should be avoided when other alternative anticoagulants are available.

There have been a number of case reports of paediatric heparin induced thrombocytopenia (HIT) in the literature and the described patients range in age from 3 months to 15 years. Heparin exposure ranged from low dose exposure during heparin flushes used in maintaining patency of venous access devices, to supratherapeutic doses given during cardiopulmonary bypass and haemodialysis. Recent studies suggest the frequency of HIT may be increased in children in the paediatric intensive care unit (2.3%) compared to children in a non-intensive care setting. A high index of suspicion is required to diagnose HIT in children, as many patients in neonatal and paediatric intensive care who are exposed to heparin have many potential reasons for thrombocytopenia and/or thrombosis. There are no data on the frequency of osteoporosis, HIT, or other hypersensitivity reactions secondary to LMWH use in children. A rare case of reversible hair loss has been described with enoxaparin.

Warfarin

Tracheal calcification or hair loss have been described on rare occasions in young children. Two cohort studies have described reduced bone density in children on warfarin for longer than one year. However, these were uncontrolled studies and the role of the underlying disorders in reducing bone density remains unclear.

CONCLUSIONS

Anticoagulation treatment in paediatric patients requires consideration of numerous variables which are different from the use of anticoagulation in adults. These include pathophysiological, pharmacological, and practical issues that need to be overcome. Current treatment guidelines are based on poor quality evidence. Data with respect to the adverse event rate from anticoagulation treatment in neonates and children is scarce, however, current information suggests this therapy has significant risks for the patient. There is an urgent need for more specific research into various aspects of anticoagulation treatment in paediatric patients, and until such research is completed, parents and children alike can only be offered uncertainty with respect to the risk:benefit ratio of our current anticoagulation strategies.

REFERENCES

The seminal papers by Andrew and colleagues in the late 1980s to early 1990s defined the concept of developmental haemostasis. However, while the concept and trends have been proven by subsequent studies, the values reported in these papers cannot be extrapolated to laboratories using different analyser and reagent systems. Each laboratory must develop their own age related reference ranges.


The largest published cohort of children receiving warfarin treatment.


Evidence based approach to antithrombotic therapeutic guidelines specific for children. The next edition which is updated significantly is in press and will be published in 2004.


One of the only published randomised controlled trials of antithrombotic treatment in children.


