



Warfarin in Children

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Background

Warfarin & Vitamin K Dependent Factors

The molecular structures of clotting factors VII, IX, X and II are modified by an enzymatic system in the presence of vitamin K. This is an essential step for the function of these factors.

The activation of coagulation factors will ultimately lead to the formation of thrombin - the key enzyme which produces fibrin, an essential component in thrombus formation. Warfarin will inhibit thrombin formation by interfering with vitamin K metabolism. The degree of inhibition will depend on the treatment intensity and the age of the child. At birth, the coagulation system is immature with plasma levels of the vitamin K dependent factors reduced to less than 50% of adult values. For this reason, warfarin therapy is rarely recommended for infants less than 2 months of age. By 6 months of age, the coagulation system is similar to the adult system and warfarin therapy can be used with careful monitoring.

Validated Regimen for Infants, Children and Teens Aiming for an INR of 2.0 - 3.0

Initial Dosing (Day 1)

If baseline INR is 1.0-1.3, start with 0.2 mg/kg orally (maximum of 5 mg). Reduce the dose to 0.1 mg/kg PO (maximum 5 mg) in patients with liver dysfunction, after a Fontan procedure, or in the presence of other hemorrhagic risk (e.g. hemodialysis).

Adjusting dosing (Day 2 - 5)

1.1 - 1.3	Repeat initial dose
1.4 - 1.9	50% initial dose
2.0 - 3.0	50% initial dose
3.1 - 3.5	25% initial dose
> 3.5	Hold until INR < 3.5 then restart according to maintenance dosing

Maintenance dosing (Day 6 onward)

1.1 - 1.4	Increase by 20% of dose
1.5 - 1.9	Increase by 10% of dose
2.0 - 3.0	No change
3.1 - 3.5	Decrease by 10% of dose
> 3.5	Hold dosing until INR is < 3.5, then restart at 20% less than previous dose.

MONITORING

General guidelines for monitoring warfarin therapy in children are similar to adult patients. The prothrombin time (PT) is the most commonly used test to monitor oral anticoagulant therapy. The PT should be reported using the International Normalized Ratio (INR). By using the INR, monitoring of warfarin is simplified and its safety is improved by the standardization of the therapeutic range, irrespective of the thromboplastin reagent used. Most laboratories now report INRs. The INR is calculated from the observed PT using the formula:

$$\text{INR} = (\text{Patient's PT in seconds} / \text{Mean of PT of normal range in seconds})^{\text{ISI}}$$

The ISI is the International Sensitivity Index for a given reagent. The mean of the normal range should be calculated by obtaining the mean of a minimum of 20 subjects' PTs with the PT determined using the laboratory's individual thromboplastin. This calculation

is done by the laboratory.

Capillary whole blood INR monitoring is feasible and safe in children.

WARFARIN DOSING

Since the half-lives of the vitamin K-dependent coagulation factors vary from 6 to 72 hrs and the half-life of warfarin is 2.5 days, changes made to the dosage will not be reflected in the INR value completely until day 3 or 4. Maintenance doses are highly dependent on patient age, vitamin K intake, intercurrent illnesses and concurrent use of other drugs. On average, children require weekly INRs with frequent changes precipitated by the introduction of antibiotics, changes in diet, and concurrent illnesses.

Warning to Parents

- No ASA, NSAIDs without consultation.
- No contact sports - but otherwise normal activities.

A physician should be consulted for the following:

- Significant changes in diet, formula intake for infants
- Introduction of new medication (e.g. antibiotics), any over-the-counter medication
- Changes in doses of on-going medications.
- Intercurrent infections
- Diarrhea and vomiting

Elective Interruption of oral anticoagulation (e.g. for surgery)

If the risk of thrombosis is high (e.g. mechanical valve), bridging with heparin is used to minimize the period without anticoagulation:

Discontinue warfarin 3- 5 days prior to surgery

- Monitor INR starting two days after stopping warfarin. Start LMWH at therapeutic doses subcutaneously when INR is below the target range. This can be done in the outpatient setting but will require advance planning to teach heparin administration.
- Check INR the morning before surgery. If INR is not below 1.5, consider 1 mg oral vitamin K and repeat INR the morning of surgery.
- Stop LMWH the morning before surgery. The last dose of LMWH should be given at least 24 hours before surgery.
- If the patient is considered at extremely high risk of thrombosis, bridge with unfractionated heparin infusion as per heparin guidelines (without initial bolus), starting 8 to 12 hours after last LMWH injection and continue until 4-6 hours prior to scheduled procedure. If UFH is given, check aPTT 1 hour prior to surgery: aPTT should be normal for age.
- After surgery, discuss with surgeon to evaluate bleeding risk. Options depending on circumstances for restarting anticoagulation include: Infusion of UFH at usual therapeutic dose starting 6-12 hours after surgery, without initial bolus; infusion of UFH at a lower dose (10 U/kg/h), without initial bolus, for the first 24 hours, increasing thereafter if there is no bleeding; infusion of UFH at usual therapeutic dose starting the day after surgery, without initial bolus; LMWH (weight-adjusted therapeutic dose) starting the day after surgery.
- Warfarin can be restarted on the night of surgery, or any subsequent night postoperatively, depending on bleeding risk and oral intake. Transition to warfarin may be achieved directly from UFH, or via LMWH for a period of time. In patients on antibiotics or other drugs, one may decide to continue LMWH until after discharge from hospital and then recommence warfarin as an outpatient. UFH or LMWH should be continued until INR is within the target range for two consecutive days.

If the risk of thrombosis is low:

- Discontinue warfarin 3- 5 days prior to surgery
- Check INR the morning before surgery. If INR is not below 1.5, consider 1 mg oral vitamin K and repeat INR the morning of surgery.
- After surgery, discuss with surgeon to evaluate bleeding risk.
- Warfarin can be restarted on the night of surgery, or any subsequent night postoperatively, depending on bleeding risk and oral intake. Usual starting dose is normal maintenance dose of warfarin for the patient. INR can be checked 3-4 days after recommencing.
- If there are concerns related to increased bleeding risk, then delaying warfarin may be appropriate.

Management of INR above the target range and emergency reversal of warfarin with or without bleeding

Elevation of the INR without significant bleeding:

Mild elevation of the INR (above the target range but < 5.0) without significant bleeding: The dose of warfarin can be omitted or lowered, with more frequent monitoring of the INR until INR is in the target range.

Moderate elevation of the INR (5.0-9.0) without significant bleeding: Omit one or more doses of warfarin, with more frequent monitoring of the INR until INR is in the target range. Resume at a lower dose. A small dose of oral Vitamin K can be given (usually 0.5 to 2 mg, higher if more rapid reversal is required).

Important elevation of the INR (above 9.0) without significant bleeding: Stop warfarin and give higher dose of Vitamin K (2–10 mg orally). Monitor more frequently and use additional vitamin K if necessary. Resume therapy at lower dose when INR is within the target range.

Rapid reversal of warfarin in the absence of significant bleeding:

The patient will require warfarin again in the near future: Administer Vitamin K 0.5-2 mg orally.

The patient will not require warfarin again in the near future: Administer Vitamin K 2-5 mg orally using the IV preparation.

Significant but not life threatening bleeding at any elevation of INR:

Stop warfarin. Give fresh frozen plasma (20 mL/kg). Supplement with vitamin K (0.5-2 mg orally or 5-10 mg by slow IV infusion, depending on the urgency of the situation). Vitamin K can be repeated every 12 hours. Consider giving prothrombin complex concentrate (Octaplex) (50 U/kg base on adult data), depending on the urgency of the situation. Recombinant factor VIIa may be considered an alternative to prothrombin complex concentrate. Vitamin K must be added when plasma, prothrombin complex concentrate or recombinant factor VIIa are administered if a sustained effect is required, because of the short half-life of these products.

Life-threatening bleeding:

Stop warfarin. Give prothrombin complex concentrate (50 U/kg) or fresh frozen plasma if prothrombin complex concentrate is not available.. Recombinant factor VIIa may be considered an alternative to prothrombin complex concentrate. Supplement with vitamin K (5-10 mg by slow IV infusion). Repeat if necessary, depending on INR. Vitamin K must be added when plasma, prothrombin complex concentrate or recombinant factor VIIa are administered if a sustained effect is required, because of the short half-life of these products. Vitamin K can be repeated every 12 hrs with persistently elevated INR.

Teenage Pregnancy:

Warfarin should not be used. It crosses the placenta and may cause embryopathy, CNS abnormalities and fetal bleeding. Teenagers need to receive appropriate counselling about these potential problems. Teenagers who become pregnant while on warfarin therapy should notify their physician immediately. In teens who require anticoagulants during pregnancy, heparin (or low molecular weight heparin) is the treatment of choice.

Immunization:

Patients can be immunized while they are on chronic anticoagulation therapy. For patient receiving warfarin, preferably immunize with INR in the lower end of the target range, using the smallest gauge needle and applying firm pressure for 5 minutes.

Adverse Effects

The types and frequency of adverse effects in children are similar to adult patients. Bleeding, usually mild, is the most important complication of anticoagulant therapy. The intensity of anticoagulation, the concomitant use of ASA, NSAIDs and the underlying clinical disorder are factors influencing the risk of bleeding. Skin rash and alopecia are uncommon adverse effects and may be managed by changing oral anticoagulants. Skin necrosis is a rare complication and usually appears within a few days of the start of oral anticoagulation therapy. Children presenting with skin necrosis should be investigated for deficiencies in Protein C and S. Osteopenia is a potential complication in children receiving long-term warfarin therapy and periodic monitoring of bone density is suggested.

Factors Affecting Warfarin's Effect

Children requiring oral anticoagulation therapy frequently have serious underlying disorders that influence their response to therapy. New medications, dosage changes in medications, diet and intercurrent viral infections are the most common factors influencing warfarin's effects. In some instances, the anticoagulant response is unpredictable. For these reasons, it is imperative to closely monitor the child's response.

This guideline was developed in collaboration with the Canadian Pediatric Thrombosis and Hemostasis Network and reviewed by T.I.G.C members, based on medical literature and on current Canadian medical practice.

References:

1. Monagle P et al. Chest 2008; 133(6):887-968S
2. Streif W et al, Blood 1999; 94(9):3007-14
3. Marzinotto V et al, Pediatr Cardiol 2000; 21:347-52