Effect of three loading doses of warfarin on the international normalized ratio for dogs

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**Objective**—To evaluate effect of 3 loading doses of warfarin sodium on the international normalized ratio (INR) for dogs.

**Animals**—18 dogs weighing between 25 and 30 kg.

**Procedure**—Dogs were randomly allocated into 3 groups and received 2, 4, or 6 mg of warfarin administered orally once a day for 2 days after surgery for bilateral iliac artery grafting. Activated partial thromboplastin (APTPT) and prothrombin times (PT) were measured before and after treatment. Prothrombin time also was reported as an international normalized ratio.

**Results**—The APTPT were not significantly different among groups before or after treatment. The INR and PT were significantly increased in all groups after treatment. The INR and PT of the 6-mg group were significantly greater than those of the 2-mg and 4-mg groups. None of the dogs had clinical evidence of bleeding.

**Conclusions and Clinical Relevance**—A warfarin loading dose of 6 mg/d can be safely administered for 2 days to dogs weighing between 25 and 30 kg. Anticoagulation can be achieved safely in dogs in 2 days by use of warfarin. The effects of warfarin can be monitored with the INR. (Am J Vet Res 2000;61:48–50)

Warfarin sodium functions as an anticoagulant by interfering with vitamin K in the formation of vitamin K-dependent coagulation factors II, VII, IX, and X, and the anticoagulant proteins C and S, which leads to accumulation of nonfunctional factors. The effect of warfarin on these factors is monitored by use of prothrombin time (PT) and reported as an international normalized ratio (INR). Recommendations have suggested that the dosage of warfarin should be adjusted to result in a PT of 1.5 times baseline; however, because of variability of thromboplastin used in the PT assay, it is now recommended to standardize PT using the INR. The INR is the prothrombin time ratio one would have obtained if the World Health Organization reference thromboplastin had been used to perform the prothrombin time on the sample test with the manual prothrombin technicue. The INR is calculated with the following equation: INR = (patient PT/control PT)\(^3\), where ISI is the international sensitivity index. The ISI is a measure of responsiveness of a given thromboplastin to reduction of vitamin K-dependent coagulation factors, compared with the international reference preparation. The optimal therapeutic range for anticoagulation therapy for humans has been reviewed by the Committee on Antithrombotic Therapy of the American College of

Chest Physicians. An INR of 2.0 to 3.0 has been recommended for all indications for anticoagulation therapy except mechanical prosthetic heart valves, for which an INR of 2.5 to 3.5 is recommended. It usually takes 5 to 7 days to reach an INR of 2.0 to 3.0, with a dosage of 4 to 5 mg of warfarin/d in humans, and it is recommended to overlap administration of warfarin treatment with administration of heparin until INR > 2.0. By extrapolation of data obtained for dogs and cats, a 30-kg dog receiving 2 to 3 mg of warfarin/d should reach an INR of 2.0 to 3.0 in approximately 5 to 7 days.

Steady state concentration for a drug can be achieved by administration of a loading dose or by gradual accumulation. A loading dose provides an amount of drug that induces an immediate effect. Use of a loading dose depends on half-life of the drug and the urgency for treatment. Anticoagulant drugs with a long half-life, such as warfarin (36 to 42 hours), are suitable for use with a loading dose, because they reach therapeutic concentrations in a short period of time and reduce risk of thromboembolism. However, the utilization of a loading dose of warfarin may increase the risk of bleeding episodes. The purpose of the study reported here was to evaluate the effect of 3 loading doses of warfarin on the INR in dogs.

**Materials and Methods**

Eighteen purpose-bred dogs weighing between 25 and 30 kg were entered into a study of iliac artery grafting with 5-mm polytetrafluoroethylene grafts. After bilateral iliac artery grafting, dogs were randomly allocated into 3 groups of 6 dogs each and received 2, 4, or 6 mg of warfarin, respectively, by oral administration once a day for 2 days to maintain patency of the iliac grafts. Dogs were maintained on heparin sodium (100 U/kg of body weight, SC) during the first 2 days after surgery. Dogs were maintained on the same diet during the duration of the study.

Determination of coagulation factors were performed before surgery and 2 days after initiation of warfarin treatment. Blood samples (2.7 ml) for coagulation factor determinations were collected from each dog’s jugular vein with a 22-gauge needle and 3-ml syringe and placed in tubes that contained buffered sodium citrate. Activated partial thromboplastin time (APTPT) and PT were measured by use of an automated analyzer. The INR were calculated with the following equation: INR = (Patient PT/Control PT)\(^3\). The PT control value was the mean of the laboratory reference range (range, 7.5 to 10.5 seconds). Tissue thromboplastin (brain) used in the laboratory had ISI = 2.02. An INR of 2.0 to 3.0 was considered an appropriate therapeutic range.

**Statistical analyses**—A Kolmogorov Smirnov test was performed to evaluate normality of the INR distribution, and 1-way ANOVA was used to evaluate effect of warfarin dose on PT, INR, and APTPT. A Fisher protected least-significant difference test was used post hoc. Level of significance was set at \(P < 0.05\).
Results

Prior to warfarin administration, APTT were not significantly different among the 2-mg (mean ± SD, 10.95 ± 0.30 seconds), 4-mg (11.13 ± 0.37 seconds), and 6-mg (10.55 ± 0.64 seconds) groups and were within reference range (10.5 to 16.5 seconds) for the Colorado State University Veterinary Teaching Hospital Clinical Pathology Laboratory. Prior to warfarin administration, PT were not significantly different among the 2-mg (8.63 ± 0.31 seconds), 4-mg (8.55 ± 0.40 seconds), and 6-mg (8.76 ± 0.34 seconds) groups and were within reference range (7.5 to 10.5 seconds). Prior to warfarin administration, INR were not significantly different among the 2-mg (0.60 ± 0.04), 4-mg (0.58 ± 0.05), and 6-mg (0.61 ± 0.04) groups.

The APTT were not significantly different 2 days after the beginning of warfarin treatment among the 2-mg (13.16 ± 2.06 seconds), 4-mg (12.23 ± 1.15 seconds), and 6-mg (14.28 ± 1.82 seconds) groups. Prothrombin times were significantly (P = 0.005) different after 2 days of treatment (2-mg group, 9.65 ± 1.19 seconds; 4-mg group, 11.90 ± 4.04 seconds; 6-mg group, 17.26 ± 4.21 seconds). The PT for the 6-mg group was longer than for the 2-mg group (P = 0.002) and 4-mg group (P = 0.016). After 2 days of treatment, INR were significantly (P = 0.003) different among the 3 groups (2-mg group, 0.85 ± 0.221 seconds; 4-mg group, 1.41 ± 0.94 seconds; 6-mg group, 2.87 ± 1.09 seconds). The INR for the 6-mg group was longer than for the 2-mg group (P < 0.001) and the 4-mg group (P = 0.009; Fig 1). After 2 days of treatment, 2 dogs in the 4-mg group and 5 dogs in the 6-mg group had an INR > 2.0, and 1 dog in the 6-mg group had an INR of 3.32. Clinical signs of bleeding in the abdominal cavity from the anastomosis or bleeding in the gastrointestinal tract or lungs were not observed.

Discussion

The American College of Chest Physicians recommends an INR between 2.0 and 3.0 for safe anticoagulation therapy with warfarin in humans and an INR of 2.5 to 3.5 for prosthetic valve replacement without increased risk for bleeding. Using similar criteria, all dogs in the study reported here had an INR within the recommended range (2.0 to 3.0). A patient is considered at risk for acute bleeding when the INR > 6.0 and will require vitamin K1 to reverse the effect of warfarin.

The APTT for each treatment group was increased, but within reference range, after 2 days of treatment with warfarin; thus, a 6-mg daily loading dose, administered for 2 days, seems to be safe and should result in an INR of 2.0 to 3.0 in a 30-kg dog. The individual effect of heparin was not determined.

Use of a loading dose of warfarin has been associated with a risk of transient hypercoagulation. Protein C, which inhibits factors VIII and V, is a vitamin K-dependent factor with half-life similar to that of factor VII (6 hours). Protein C concentration is significantly reduced 36 hours after administration of a 10-mg loading dose of warfarin in humans, which increases risk for hypercoagulation in the early phase of warfarin treatment. In the study reported here, plasma protein C concentrations were not measured, but, because APTT were not significantly decreased after 2 days of warfarin treatment, it seems unlikely that dogs were in a hypercoagulable state.

Dose response to warfarin is influenced by pharmacokinetic factors (differences in absorption or metabolic clearance) and pharmacodynamic factors (differences in hemostatic responses to various concentrations of warfarin). Phenylbutazone, metronidazole, and trimethoprim-sulfamethoxazole potentiate the anticoagulation effect of warfarin by inhibiting its clearance. Barbiturates and rifampicin decrease the anticoagulation effect of warfarin by increasing its metabolic clearance via hepatic oxidase. Second- and third-generation cephalosporins potentiate the anticoagulation effect of warfarin by inhibiting vitamin K metabolism.

Risk of bleeding during warfarin treatment can be increased by any drugs that inhibit platelet function (eg, aspirin, nonsteroidal antiinflammatory drugs, and penicillins). The amount of vitamin K received from the diet is also an important factor; dose of warfarin should be adjusted by checking INR after the animal begins to eat following surgery. It is recommended to maintain the same diet to avoid changes in vitamin K daily intake. Dogs of the study reported here received the same diet and the same antibiotic (first-generation cephalosporin) for 5 days after surgery.

Sensitivity of INR is a function of ISI. The INR system is based on ISI values derived from plasma of patients stabilized for ≥ 6 weeks. The early anticoagulant effect of warfarin is primarily attributable to depletion of factor VII (half life, 6 hours), whereas later effects are primarily attributable to depletion of factors II and X (half life, 72 hours). Therefore, the INR lacks sensitivity, especially in the first days of anticoagulation treatment. The use of a responsive thromboplastin with a lower ISI (< 1.2) should increase sensitivity of the INR. To avoid this problem, it has been recommended to use PT to monitor patients in the early phase of anticoagulant treatment and INR in the later phase. Nevertheless, the American College of Chest Physicians still recommends use of the INR instead of PT, even in the early phase of anticoagulant treatment.

A warfarin loading dose of 6 mg/d for 2 days in a 30-kg dog should induce an increase of the INR to a value
between 2.0 and 3.0. Heparin should be administered concurrently. After 2 days, administration of heparin should be discontinued, and the loading dose of warfarin should be reduced by half. Thereafter, the patient should be monitored daily by evaluation of the INR.

References