Warfarin

Synonym: coumafene
Chemical name: 4-hydroxy-3-(3-oxo-1-phenylbutyl)coumarin
CAS: 81-81-2
MF: $C_{19}H_{16}O_4$
FW: 308.3
Solubility: warfarin is practically insoluble in water and benzene; moderately soluble in alcohols, and readily soluble in acetone and dioxane. The sodium salt is fully soluble in water [1].

Major uses
Warfarin is a synthetic vitamin K antagonist used in anticoagulation therapy. It is also used as a rodenticide [2].

Human toxicity
The primary effect of warfarin overdose is prolongation of protrombin time, and subsequent risk of hemorrhage. Clinical manifestation begins a few days or weeks after ingestion, and includes i.e. gastrointestinal bleeding, hematuria, back pain, mucous membrane hemorrhage, abdominal pain, vomiting, intracranial hemorrhage, hemorrhagic shock, and even death at severe intoxications.

Persons with a history of blood disorders with bleeding tendencies would be expected to be at increased risk from exposure. Hereditary resistance of people to warfarin, as well as suspected hereditary susceptibility, has been reported [2].

Therapeutic dose of warfarin is 2 to 10 mg/day. An estimated dose of 0.075 to 0.48 mg/kg may produce a peak blood warfarin concentration of 0.5 to 3 mg/l [2].

The lowest oral lethal dose reported in humans is from 6 to 15 mg/kg [1, 2].

The plasma concentrations of warfarin after an overdose (two sub-lethal cases) varied between 13.5 and 111.0 mg/l [3].

Carcinogenicity: No data are available to assess the carcinogenic potential of warfarin [2].

Kinetic data
Absorption: warfarin is almost completely and rapidly absorbed from the gastrointestinal tract [4]. Absorption may also occur by inhalation and through the skin [2].

Bioavailability: high (no numbers available) [4].

Kinetics: first order [4].

Volume of distribution (Vd): 0.11 l/kg [4].

Protein binding: 99% [4].

Blood peak concentration is reached in 3-9 h [4].

Elimination half-life: 22-96 h [4].

Passage of blood-brain barrier: restricted [4].

Metabolism and excretion
Warfarin is metabolized by hepatic cytochrome P450 microsomal enzymes. In man, the main metabolites of warfarin, found in the urine, include 6- and 7-hydroxywarfarin and two aliphatic side-chain alcohols [1].

Excretion: the metabolites mentioned above are conjugated with glucuronic acid, and excreted in the urine and feces [1].

Mechanisms of action
Warfarin has two main effects: it inhibits synthesis of vitamin K-dependent blood coagulation/clotting factors (one of them is factor VII, proconvertin); and it inhibits the synthesis of prothrombin (factor II) in the liver [5].

Toxicological mechanisms
An excessive amount of warfarin leads to depression of prothrombin activity, resulting in hemorrhage in capillaries, and circulatory failure (most often reasons of death) [1, 5].

Adequacy of treatment with warfarin usually is followed by measuring prothrombin time. In case of poisoning, the prothrombin time is greatly prolonged.

The effective treatment of poisoning with warfarin is administration of massive doses of vitamin K_1 [5].

Target organs: liver; vascular system (blood vessels/capillaries) [4].

References
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