Effects of Multiple Administrations of Warfarin on Drug Metabolizing Enzyme Activities in Rats

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Rats are more susceptible to multiple administrations of warfarin with small doses than a single administration of large dose. The lethal dose in total with multiple administrations is reported to be about one third of the lethal dose at the single administration. Three hypotheses were tested to elucidate the mechanism of this phenomenon in this study : Multiple administrations of relatively low doses of warfarin may result in (1) general deterioration of liver function, (2) decrease in albumin synthesis which in turn results in the increase in free warfarin concentration, or (3) decrease in warfarin metabolizing enzyme activity.

Rats were treated with a single dose (15 mg/kg) of warfarin or multiple doses (1.5mg/kg/day) of warfarin once each day for 4 days. Plasma samples were tested for the sign of hepatopathy and concentrations of albumin in these samples were determined. Liver microsomes were prepared to investigate activities of cytochrome P450 isozymes, which metabolize warfarin as well as other chemicals.

The mortality rate of rats with multiple warfarin administration was significantly higher than that of rats received a single warfarin administration. Heavy bleeding was observed in all the rats died during this experiment. Apparently they died from the anticoagulatory activity of warfarin. Blood tests revealed that there was no difference in activities of aspartate aminotransferase and alanine aninotransferase, the indicator enzymes of hepatopathy, and that there was no difference in albumin concentrations between these two groups of rats with different warfarin administration schedule. The ability of the liver microsomes to metabolize warfarin was significantly lower in rats received multiple administrations of low doses of warfarin than in rats with a single dose of warfarin. Total P450 contents in liver microsomes from rats with multiple administrations of warfarin were significantly lower than those in rats with a single administration. The enzyme activities mainly catalyzed by P450 2B1, 2C11, or 3A2 were significantly decreased by the multiple administrations of warfarin.

Taken altogether, it is concluded that the multiple administrations of warfarin at sublethal dose result in selective decrease in several P450 isozymes which metabolize warfarin, and this in turn leads rats to death from elevated levels of unmetabolized warfarin.