Ticrynafen Effect on Warfarin Protein Binding in Human Serum

Keyphrases □ Ticrynafen—effect on warfarin protein binding, human serum □ Protein binding—warfarin to serum protein, effect of ticrynafen, humans □ Warfarin—serum protein binding, effect of ticrynafen, humans □ Antihypertensive agents—ticrynafen, effect on warfarin protein binding, human serum □ Anticoagulants—warfarin, serum protein binding, effect of ticrynafen, humans

To the Editor:

Ticrynafen[1] [2,3-dichloro-4-(2-thienylcarbonyl)-phenoxyacetic acid] is a new antihypertensive, diuretic, and uricosuric agent (1). About 99.5% of this weak acid is bound to human serum proteins in the therapeutic drug concentration range (2). Serious drug interactions between ticrynafen and the coumarin anticoagulants ethyl biscoumacetate and acenocoumarol have been reported, with anticoagulant potentiation and hemorrhages (3–5). It has been suggested that these interactions resulted from anticoagulant displacement from serum protein binding sites by ticrynafen and that this might also occur with warfarin (2–5).

We determined the ticrynafen effect on warfarin protein binding in human serum over a wide range of ticrynafen concentrations. Blood was obtained from two healthy adult male donors, serum was separated and pooled, and racemic ^{14}C-warfarin (2 μg/ml) was added. Ticrynafen[2] was dissolved in 50 μl of ethanol, and pH 7.4 sodium phosphate buffer (0.134 *M*) was added to yield 5 ml of solution containing 10–200 μg of ticrynafen/ml. Ticrynafen-free buffer solutions contained the same concentration of ethanol. Plasma containing warfarin was dialyzed at 37° to equilibrium against these solutions. Warfarin was then extracted from both phases, separated from impurities and degradation products by TLC, and assayed by scintillation spectrometry as previously described (6, 7).

The results are shown in Table I. Warfarin, in the absence of ticrynafen, was 99.288% bound (results of three dialysis experiments were 99.265, 99.297, and 99.301%). Ticrynafen (10–200 μg/ml) had no apparent effect on warfarin serum protein binding. Essentially identical results were obtained when both warfarin and ticrynafen were added to serum (without ethanol), and these serums were dialyzed against buffer only. The warfarin concentration used in this study was in the upper therapeutic concentration range (8, 9); the concentrations of ticrynafen ranged from therapeutic (~10–40 μg/ml) to far above therapeutic concentrations (1, 2). Since both drugs are extensively protein-bound weak acids, displacement effects may occur at even higher concentrations of either compound or in diluted plasma or diluted albumin solutions.

The results indicate that warfarin will not be significantly displaced from serum protein binding sites by ticrynafen under the usual therapeutic conditions. They do not rule out other interactions such as inhibition of warfarin metabolism, direct effects of ticrynafen on the blood coagulation process, and effects of ticrynafen metabolites.

Table I—Effect of Ticrynafen on Warfarin Protein Binding in Human Serum [a]

Ticrynafen Concentration, μg/ml	Warfarin Free Fraction[b] × 100	Warfarin Free Fraction Ratio[c]
0	0.712	1.00
10	0.688	0.97
20	0.655	0.92
30	0.710	1.00
40	0.771	1.08
50	0.695	0.98
100	0.751	1.05
200	0.725	1.02

[a] Determined by equilibrium dialysis at 37°. Initial warfarin concentration was 2 μg/ml. [b] Mean of two or three determinations. [c] Free fraction divided by free fraction in the absence of ticrynafen.

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Received November 15, 1978.
Accepted for publication December 27, 1978.
Supported in part by Grant GM 20852 from the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, MD 20014.

Comparison of Antineoplastic Activity of Aminoethylaminoanthraquinones and Anthracycline Antibiotics

Keyphrases □ Antineoplastic activity—aminoethylaminoanthraquinones, doxorubicin, daunorubicin, and cardiotoxicity □ Antineoplastic agents—aminoethylaminoanthraquinones, doxorubicin, daunorubicin, and cardiotoxicity □ Aminoethylaminoanthraquinones—antineoplastic activity and cardiotoxicity, compared to doxorubicin and daunorubicin □ Cardiotoxicity—evaluated, aminoethylaminoanthraquinones, doxorubicin, daunorubicin

To the Editor:

The anthracycline antibiotics doxorubicin and daunorubicin are among the most important antineoplastic agents studied in recent years. Both antibiotics demon-

[1] SKF-62698, Selacryn.
[2] Supplied by Smith Kline & French Laboratories, Philadelphia, Pa.

0022-3549/79/0300-0393$01.00/0