Multiple doses of trandolapril do not affect warfarin pharmacodynamics

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Objective. The effects of multiple doses of trandolapril (a new angiotensin-converting enzyme inhibitor) on the pharmacodynamics of a single 25 mg dose of warfarin were investigated in 19 men.

Design. A double-blind, placebo-controlled cross-over design was used. The study consisted of two periods of 13 days each, during which subjects received either trandolapril 2 mg or placebo once daily according to a randomisation plan. Warfarin was given on day 8 of each of these periods.

Setting. The study was carried out at the Hoechst Research Centre for Clinical Pharmacology, Department of Pharmacology, University of the Orange Free State, Bloemfontein.

Patients. Nineteen healthy white men aged between 18 and 28 years and weighing between 65 and 98 kg volunteered for the study.

Outcome measures. Prothrombin time (PT) and coagulation factors II, VII, IX and X were measured before and sequentially up to 6 days after warfarin administration. Areas under the PT and coagulation factor time curves for warfarin + trandolapril were compared with the corresponding areas for warfarin + placebo. The two treatment combinations were also compared at each measuring time.

Results. The point estimate for the ratio of the treatment means of warfarin + trandolapril relative to warfarin + placebo for PT was 97% (90% confidence interval: 90% - 103%). The corresponding value for factor VII was 97% (90% confidence interval: 91% - 102%).

Conclusion. The concomitant administration of trandolapril did not affect the pharmacodynamic effects of warfarin.

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Warfarin is commonly used as an oral anticoagulant and is frequently prescribed together with other drugs. Since warfarin has a narrow therapeutic index, its concomitant use with other drugs may result in interference with its action and consequent haemorrhage or spontaneous thrombosis. The oral anticoagulants are vitamin K analogues and they act as competitive antagonists to this vitamin at the liver cell, thereby inhibiting the post-ribosomal step in the synthesis of factors II, VII, IX and X, resulting in the formation of inactive precursor proteins.[1,2] It takes at least 3 days for the full effect of vitamin K antagonism to manifest itself since the time required for the activity of each factor to reach steady state after commencement of therapy is determined by its half-life. The plasma concentration of factor VII, which has the shortest half-life, is the first to decrease and is followed by those of factors IX, X and II.[1] The aim of our study was to investigate the effects of multiple doses of trandolapril, a new angiotensin-converting enzyme inhibitor, on the pharmacodynamics of a single dose of warfarin. For this purpose the approach of Kroon *et al.*[3] and Duursema *et al.*[4] was used. The prothrombin time (PT) and the activity of factors II, VII, IX and X after medication with warfarin and placebo were compared with those after medication with the warfarin and trandolapril combination.

Materials and methods

The study was approved by the Ethics Committee of the University of the Orange Free State and the South African Medicines Control Council and was conducted in accordance with the guidelines of the Declaration of Helsinki. Nineteen healthy white men aged between 18 and 28 years and weighing between 65 and 98 kg gave written consent before participating in this study. They abstained from alcohol and non-trial medication for the duration of the study. A two-way, double-blind, randomised cross-over design was used.

In pilot studies the inhibition of factors VII and X was greater after an initial dose of 25 mg warfarin than after subsequent doses 3 weeks later.[4] A similar observation was also made by Stirling *et al.* in 1982.[5] For this reason a priming dose of 25 mg warfarin alone was given to all volunteers on day 1 of the study.

Trandolapril or placebo was given on a randomised basis daily on days 8 through 20 and 22 through 34. The dose of trandolapril was 2 mg and it was given under supervision daily before breakfast at 07h30.

Warfarin sodium (25 mg) was also administered orally on days 15 and 29, i.e. on the eighth day of treatment with trandolapril/placebo. Factors II, VII, IX and X activity in plasma and the PT were measured before and 12, 24, 48, 72, 96, 120 and 144 hours after warfarin administration. The study design is shown in Fig. 1.

Analytical methods

PT, expressed in seconds, was determined by a human thromboplastin/calcium reagent system (Western Diagnostics). Blood samples (4,5 ml) were collected in a plastic syringe and added to a plastic tube containing 0,5 ml

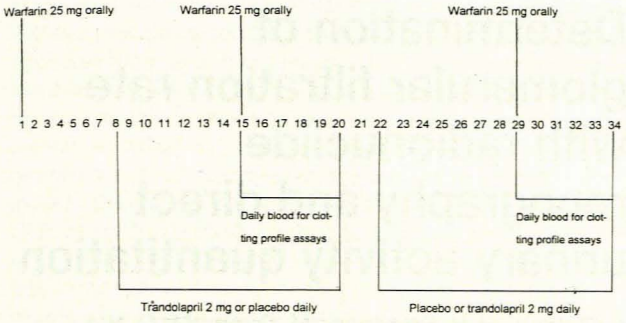

Fig. 1. Study design.

3,13% w/v sodium citrate as anticoagulant. In the laboratory, the cascade was initiated by the addition of calcium plus the activating agent (tissue thromboplastin which contains phospholipid and a tissue factor), and the clotting time calculated relative to the clotting time of control plasma treated in the same way as the test.

Factors II, VII, IX and X were quantitatively assayed with an ACL coagulation instrument (Instrumentation Laboratories) by means of the Western Diagnostics Quantiwest II, VII, IX and X methods, respectively. The plasma of these types of Quantiwest reagents is deficient in the relevant factor, but contains adequate concentrations of the other factors necessary for coagulation. Assays are based on a comparison of the degree of correction of the PT of the factor-deficient plasma by the test plasma or standard plasma. A range of dilutions of the standard and test plasmas was prepared with Owrens Veronal buffer (pH 7), and the PT coagulation test was performed on each sample. The mean clotting time of each dilution of test and standard plasma was plotted against the percentage dilution on a log-log graph. The first dilution of the standard plasma was regarded as equivalent to 100%. The clotting times of the test dilutions were converted to coagulation factor activity by extrapolation from the test to the standard curve.

Method of statistical analysis

In order to investigate the effects of trandolapril on warfarin, the effects of treatment groups warfarin + trandolapril and warfarin + placebo were compared by analysis of variance of the area under the relevant clotting parameter-time data pairs (area under the curve (AUC)). Point estimates and 90% confidence intervals were calculated for the ratio of the treatment means of warfarin + trandolapril relative to warfarin + placebo for the areas under the curve. The same analysis was also performed on the data at each of the various sampling times.

Results

The effects of the two treatment combinations, warfarin + trandolapril and warfarin + placebo, on the mean PT and factor VII concentration time profiles are illustrated in Figs 2 and 3.

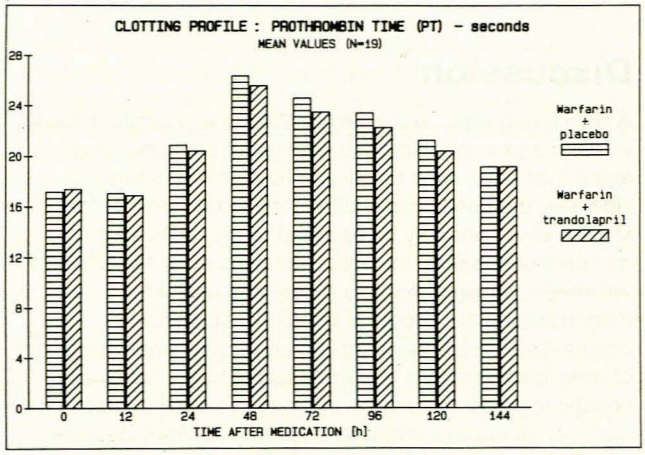

Fig. 2. Prothrombin time(s) measured sequentially after medication with warfarin + placebo and warfarin + trandolapril.

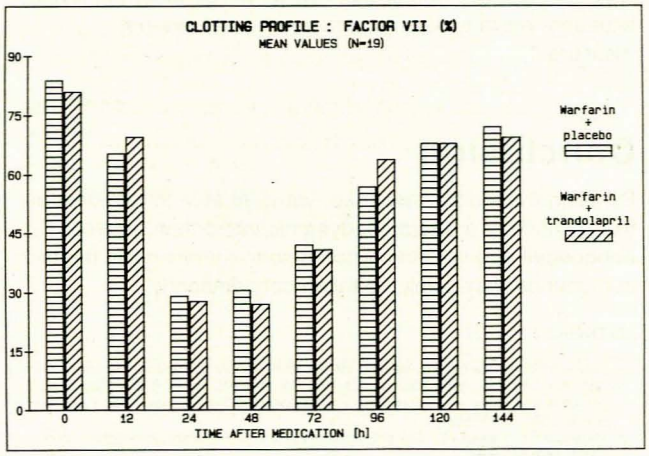

Fig. 3. Factor VII activity (%) measured up to 144 hours after medication with warfarin + placebo and warfarin + trandolapril.

The mean AUC values, treatment ratios, point estimates of the ratios and the 90% confidence intervals are given in Table I. The results revealed that the differences between treatments were negligible. This finding was confirmed by

Table I. Mean AUC values for PT and factor VII, treatment ratios, point estimates of ratios and 90% confidence intervals

Variable	Treatment	Mean AUC (SD)	Point estimate of ratio $\frac{W+T}{W+P}$ (%)	90% confidence interval (%)
PT	W+P	134 (46,4) day.sec	97	90 - 103
	W+T	129 (27,7) day.sec		
Factor VII	W+P	318 (112) %.day	97	91 - 102
	W+T	307 (89,4) %.day		

W+ P = warfarin + placebo; W+T = warfarin + trandolapril.

comparison of the treatments at each of the various sampling times.

Changes in the activity of factors II, IX and X were very similar to those observed for factor VII, but since factor VII is known to be more sensitive as an indicator of warfarin-drug interaction, only factor VII data are presented.

Discussion

A similar approach to that of our study, i.e. a single dose of warfarin and a multiple-dose regimen of the interacting agent, has been used by several other investigators.[3,6-11] However, the conflicting results obtained in some of these studies could possibly be ascribed to the relatively small numbers of subjects enrolled. Duursema *et al.*,[4] by using 17 volunteers, showed that this model was useful for demonstrating the effects of drugs like vitamin K (a competitive warfarin antagonist), cholestyramine (an inhibitor of absorption from the gastro-intestinal tract), rifampicin (a hepatic microsomal enzyme inducer), cimetidine (a hepatic microsomal enzyme inhibitor) and aspirin, which displaces protein-bound drugs from their binding sites.

Our study was a pharmacodynamic one and, since the effects of interactions between warfarin and other drugs on coagulation factors are the important issues determining whether haemorrhage or thrombosis will occur in the clinical situation, warfarin plasma concentrations were not measured.

Conclusion

By using the model described, we were able to demonstrate the absence of a pharmacodynamic interaction between trandolapril and warfarin. According to these results the two compounds may safely be taken concomitantly.

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