Investigations into the potential effects of multiple dose ketorolac on the pharmacokinetics and pharmacodynamics of racemic warfarin

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- 1 The potential interaction between racemic warfarin given as a 25 mg single oral dose and chronically administered ketorolac was studied in 12 young healthy male volunteers.
- 2 Ketorolac produced no major change in the pharmacokinetics of (R)- or (S)-warfarin.
- 3 Ketorolac did not alter the pharmacodynamic profile of racemic warfarin.
- 4 Ketorolac increased template bleeding time by a factor of 1.35 as compared with placebo.
- 5 The results suggest that the ketorolac–warfarin interaction is unlikely to be of major clinical significance; however, combined use of ketorolac and warfarin in patients should be undertaken with due caution and appropriate monitoring.

Keywords (R)- and (S)-warfarin ketorolac drug–drug interaction pharmacokinetics pharmacodynamics haematological variables

Introduction

Ketorolac is a pyrrolo-pyrrole derivative currently under development as an analgesic for use in the treatment of post-operative and cancer pain.

In vitro ketorolac has been shown to be an inhibitor of platelet aggregation, being 37 times as active as aspirin in inhibiting collagen-induced platelet aggregation and over 28 times more potent than aspirin in inhibiting aggregation induced by arachidonic acid. This inhibition of platelet aggregation is reflected by *in vivo* observations of a 32% increase in template bleeding time in patients receiving 10 mg ketorolac four times daily (Spowart *et al.*, 1988).

Warfarin is still the most widely prescribed long-term oral anticoagulant in the United Kingdom and warfarin therapy may frequently be initiated peri-operatively (e.g. for primary or secondary prevention of deep vein thrombosis and/or pulmonary embolism). The independent pharmacological action of ketorolac on a separate limb of the haemostatic mechanism from that

which is affected by warfarin raises the potential of a clinically important interaction occurring when warfarin and ketorolac are co-administered.

The present investigation was undertaken to assess the potential safety of the co-administration of ketorolac and warfarin, paying particular attention to potential changes in the pharmacological profile of warfarin and to changes in the pharmacokinetics of the individual warfarin enantiomers.

Methods

Subjects

Twelve young healthy male volunteers took part in the study. Their average height, weight and age were 179 cm (range: 166–194), 73 kg (range: 56–94) and 25 years (range: 20–32), respectively. All volunteers were judged to be healthy as a result of a physical examination

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both before and after the study. The results of biochemical tests, pre- and post-study, were within the normal ranges for the age group. Each volunteer was given a detailed description, both verbally and in writing, of the purpose of the study, the discomfort and likely risks involved and the procedures to be followed. Each gave their written informed consent before entering the study. The study was reviewed and authorised by the Medeval Ethics Committee, a voluntary body operating independently of the company.

The haematological status, with respect to clotting and bleeding times, of all 12 volunteers was assessed prior to commencement of the study (i.e. in a drug-free state). Of the 12 volunteers commencing the study, 10 successfully completed all phases.

Study design

The study was of a double-blind two-way randomised cross-over design.

Each volunteer received a 12 day multiple oral dosing regimen of either ketorolac in a regimen (10 mg four times daily) facilitating the attainment of steady state by day 6 and mimicking a clinically relevant dosing schedule (Jung *et al.*, 1988) or ketorolac placebo (four times daily), of identical appearance to the active medication. On day 6 of ketorolac or placebo administration each volunteer received a single 25 mg oral dose of racemic warfarin. Blood samples for measurement of the individual warfarin enantiomer ((R) and (S)) concentrations in plasma were taken at 0, 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144 and 168 h post-warfarin dosing. Following the blood sampling schedule, a wash-out period of at least 14 days was allowed before an individual received the alternate regimen.

Analysis of (R)- and (S)-warfarin in plasma

Warfarin enantiomers were measured simultaneously in plasma by h.p.l.c. analysis with fluorescence detection (Banfield & Rowland, 1984). Ketorolac was found not to interfere with the measurement of warfarin in plasma.

Briefly, the analytical method involved solvent extraction of the warfarin enantiomers from plasma followed by the formation of diastereoisomers by reaction with carbobenzyloxy-L-proline in the presence of dicyclohexylcarbodiimide and imidazole. The diastereoisomers were then separated by normal phase h.p.l.c. and, following post-column aminolysis with n-butylamine, measured using fluorescence detection.

The analytical method was validated prior to

sample analysis. The assay was found to be linear over the entire concentration range (0.1–2 mg l⁻¹) studied for both (R)- ($r^2 = 0.996$) and (S)-warfarin ($r^2 = 0.991$) with the coefficients of variation associated with the determination of the upper and lower concentrations being 5.5% ($n = 10$) and 7.9% ($n = 8$) for the (R) enantiomer, and 5.1% ($n = 10$) and 4.3% ($n = 8$) for (S)-warfarin. The assay limit for both enantiomers was defined as the concentration of the lowest calibration standard (0.1 mg l⁻¹). All plasma samples from both phases for a given individual were analysed on the same occasion.

Assessment of haematological changes

The haematological status of the volunteers was measured using a variety of indices.

The prothrombin time was measured by the method of Quick (1966) at 0, 4, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144 and 168 h after warfarin dosing. Factor VII clotting time was measured (Toon *et al.*, 1987) as were kaolin cephalin clotting time (KCCCT), and β -thromboglobulin concentrations at 0, 24 and 36 h post-warfarin dosing.

Template bleeding time was assessed in all cases by the same technician who had experience with the technique. A dual measurement template on the anterior surface of the forearm was used with the mean of the two readings being taken as the bleeding time. Template bleeding was measured prior to commencement of the study, immediately preceding and 36 h after warfarin dosing. Volunteers with control template bleeding times greater than 450 s were not admitted into the study.

Measurement of warfarin plasma protein binding

Plasma protein binding of warfarin in the absence and presence of ketorolac was measured using ultracentrifugation. Plasma samples (1.5 ml) taken at times approximating to maximum and minimum plasma ketorolac concentration were spiked with 1.25 μ Ci (148 μ Ci mg⁻¹) of [¹⁴C]-warfarin. After vortex mixing, 1.3 ml of the plasma sample was placed into a polyallomer ultracentrifuge tube and centrifuged at 50,000 rev min⁻¹ at 37° C for 15 h. Following centrifugation, 100 μ l of the clear supernatant (plasma water containing unbound warfarin) was taken from each ultracentrifuge tube, in duplicate, and added to 5 ml of scintillant. Of the residual 'spiked' plasma (not centrifuged; containing total (bound plus unbound) warfarin) 50 μ l was added to 5 ml of scintillant. After thorough mixing each vial was counted for 2 min.

The fraction of warfarin not bound to plasma proteins (unbound fraction; f_u) was calculated as:

$$f_u = \frac{d \min_{\text{unbound}}^{-1} / 100 \mu\text{l}}{d \min_{\text{total}}^{-1} / 100 \mu\text{l}}$$

where the $d \min^{-1}$ values were the means of the duplicate analysis.

Pharmacokinetic analysis

As the oral absorption of warfarin is rapid compared to its elimination, pharmacokinetic parameters associated with the disposition of the warfarin enantiomers were calculated disregarding the absorption phase. The plasma warfarin concentration-time data associated with the terminal (elimination) phase were subjected to weighted non-linear least squares analysis. The observed plasma concentrations were weighted by $\hat{y}^{-1}$, where $\hat{y}$ is the predicted plasma warfarin concentration obtained from the regression analysis.

The elimination rate constant (k) was obtained directly from the regression analysis and the elimination half-life ($t_{1/2}$), was calculated from:

$$t_{1/2} = \frac{0.693}{k} \quad (1)$$

The apparent total clearance (CL/F) was calculated from:

$$CL/F = \frac{\text{Dose}}{\text{AUC}} \quad (2)$$

where CL is the total clearance, F is the oral bioavailability, Dose is the administered oral dose of either (R)- or (S)-warfarin (12.5 mg) and AUC is the total area under the respective enantiomer concentration-time profile between time 0 and infinity. The AUC was calculated using the linear trapezoid approximation from time 0 to t , the last sampling time. The additional area from t to ∞ was calculated as Ct/k , where Ct is the predicted enantiomer concentration at time t and k is as previously defined. The extrapolated area accounted for less than 10% of the total.

The apparent volume of distribution (V_z/F) was calculated as:

$$V_z/F = \frac{CL/F}{k} \quad (3)$$

The maximum plasma enantiomer concentration (C_{max}) and the time taken to achieve that con-

centration (t_{max}), were direct experimental observations.

Statistical analysis

The data were analysed both by treating the first period as a parallel group study and by a two period cross-over design analysis with estimation of the carryover effect. P values were derived from two-sided Student's t -tests.

Wherever repeated measurements were made within each treatment period, analysis of variance was also used on an appropriate additive model. P values were derived from one-sided Fisher's F tests. It should be noted that the additive model aliases all carryover effect and so the analysis of variance forces an assumption of no carryover effect.

Results

Subject reconciliation

Twelve male subjects entered the study but only 10 subjects completed both periods. One subject (assigned to ketorolac) complained of stomach cramps on the second day of dosing in the first period, and subsequently withdrew from the study. Physical examination showed no abnormality other than mild epigastric tenderness. The results of haematological and biochemical tests were unchanged from the pre-trial values. This subject was excluded from all analyses of effect; it was not possible to replace him.

Of the remaining 11 subjects, one completed the first period uneventfully but was found to have a bleeding time of 611 s at the end of the baseline phase of the second period just prior to warfarin dosing. Since this value was above the pre-determined upper limit of 450 s considered safe for continuation, warfarin was not administered. Trial medication (subsequently found to be active ketorolac for this period) was continued. The bleeding time 12 h later was 583 s, still above the pre-set safety limit, and so the subject was withdrawn from the study. The template bleeding time had been 240 s at baseline and 270 s in the first period on placebo prior to warfarin. The response with ketorolac may be idiosyncratic, although follow-up template bleeding times were not obtained. The subject could not be replaced. Where appropriate, the data from the first period (in which placebo was received) have been used in the subsequent analysis.

All subjects fulfilled the entry criteria for age and weight.

Table 1 Average haemostatic variables following the administration of a single 25 mg oral dose of racemic warfarin to healthy male volunteers in the presence and absence of chronic ketorolac administration

Parameter	Time post-warfarin (h)	Placebo	Ketorolac	Statistics
Area under the prothrombin time-time curve (AUC _{PT} ; s.h $\pm$ s.d.)		3243 $\pm$ 255	3310 $\pm$ 338	$P = 0.069$
Maximum prothrombin time (P _{Tmax} ; s $\pm$ s.d.)		24.7 $\pm$ 3.0	25.6 $\pm$ 4.9	NS
Time to achieve P _{Tmax} (t _{PTmax} ; h $\pm$ s.d.)		45.6 $\pm$ 14.0	42.0 $\pm$ 10.2	NS
Factor VII clotting time (s $\pm$ s.d.)	pre-warfarin	14.4 $\pm$ 0.49	14.1 $\pm$ 0.47	*
	24	20.5 $\pm$ 2.3	20.3 $\pm$ 2.7	
	36	21.4 $\pm$ 3.4	21.4 $\pm$ 3.9	
Template bleeding time (min $\pm$ s.d.)	pre-warfarin	4.84 $\pm$ 0.78	6.86 $\pm$ 1.64	$P = 0.019$
	36	5.23 $\pm$ 0.92	6.18 $\pm$ 1.62	
β -thromboglobulin concentrations (ng ml ⁻¹ $\pm$ s.d.)	pre-warfarin	93.7 $\pm$ 61.4	123.3 $\pm$ 55.4	*
	24	70.1 $\pm$ 42.2	70.9 $\pm$ 43.5	
	36	104.1 $\pm$ 36.2	108.1 $\pm$ 53.8	
Kaolin cephalin clotting time (KCCT; s $\pm$ s.d.)	pre-warfarin	51.4 $\pm$ 10.6	49.4 $\pm$ 5.7	*
	24	56.1 $\pm$ 7.9	56.1 $\pm$ 7.0	
	36	48.4 $\pm$ 3.7	47.6 $\pm$ 3.2	

*No significant effect of ketorolac; significant time effect (repeat measures ANOVA)

Figure 1 Average augmented prothrombin time-time profiles following the administration of a single 25 mg oral dose of racemic warfarin to healthy male volunteers in the absence (placebo; ●) and presence (○) of chronic ketorolac administration.

Haematology

The mean values for the various haemostatic variables are shown in Table 1. The prothrombin time-time profiles in the absence and presence of chronic ketorolac administration are shown in Figure 1.

Maximum prothrombin time (PT_{max})

No effect of ketorolac was shown by either a first period or crossover analysis. There was a statistically significant difference ($P = 0.004$) between measurements in the first and second periods, such that the latter were lower regardless of the treatment received.

Time to reach maximum prothrombin time

The mean time when the maximum prothrombin time was reached ranged from 38–55 h. Again, no significant effect of ketorolac relative to placebo was shown by either a first period or a crossover analysis. In the crossover analysis, there was a statistically significant period effect ($P = 0.0480$) such that the second period showed a longer time to reach PT_{max} irrespective of the treatment received.

Area under the PT time curve (AUC_{PT})

There was again a statistically significant ($P = 0.001$) period difference in the crossover analysis, such that the AUC_{PT} was less in the second period than the first. This was consistent with

the previously noted effect of a lower PT_{max} in the second period. Ignoring any carryover effect, AUC_{PT} was significantly less ($P = 0.010$) on ketorolac compared to placebo. However, the estimated carryover effect was large ($P = 0.062$).

The first period analysis showed a treatment difference in the opposite direction (so that AUC_{PT} was larger in the presence of ketorolac), although the difference was not statistically significant ($P = 0.069$).

Factor VII clotting time

Factor VII clotting times pre-warfarin tended to be slightly lower on ketorolac (mean 14.1 s) than on placebo (14.4 s) but this difference was not of statistical significance.

At 24 h post-warfarin dosing the mean placebo values had increased to 20.5 s. The overall mean on ketorolac was 20.3 s, but this was derived from a mean of 22.0 s for those five patients who had ketorolac as their first treatment and a mean of 18.6 s for the other five patients who had ketorolac as their second treatment. Therefore, in the statistical analysis this produced a highly significant difference between treatment periods, although there was no significant difference between treatments.

At 36 h after warfarin there were no statistically significant differences. In the analysis of variance, large differences between the mean Factor VII clotting times pre-warfarin and those post-warfarin appear as a statistically significant effect but the difference between treatments remained clearly non-significant at all three times.

Kaolin cephalin clotting time (KCCT)

The pre-warfarin KCCT measurements showed a statistically significant period effect, with longer times in the second period irrespective of group assignment. There were no other significant differences. The same significant period effect was seen in the 24 h post-warfarin dosing KCCT measurement, although the magnitude was somewhat less; in the 36 h post-warfarin warfarin KCCT measurement this trend continued and the period effect was not significant. No statistically significant treatment differences were seen at either time point.

The analysis of variance showed a tendency for the difference between treatments to be greater pre-warfarin than post-warfarin, but none of the differences was statistically significant.

β -thromboglobulin concentration

Pre-warfarin β -thromboglobulin concentrations were not significantly different between treatments, but there was a markedly significant period effect such that all values were higher in the second period irrespective of treatment.

There were no significant differences at either 24 or 36 h post-warfarin.

Analysis of variance showed no significant differences between the treatments, but confirmed the difference between the periods.

Template bleeding time

Template bleeding time was significantly higher on ketorolac (mean 6.5 min) than placebo (mean 4.8 min) before warfarin was given, both by the first period analysis and the crossover analysis. There was no evidence of carryover or period effects in the latter case. The treatment difference between placebo and ketorolac was estimated as 1.98 min ($P = 0.037$) by the first period analysis and 1.65 min ($P = 0.019$) by the crossover analysis.

The treatment differences 36 h following warfarin were in the same direction but somewhat smaller, being 1.44 min ($P = 0.017$) by first period analysis and 0.90 min ($P = 0.26$, not significant) by crossover analysis.

Warfarin pharmacokinetics

The average plasma warfarin concentration time profiles in the presence of ketorolac and placebo are shown for the (R) enantiomer and for the (S) enantiomer in Figure 2. The mean parameters defining the pharmacokinetics of (R)- and (S)-warfarin in the absence and presence of ketorolac are shown in Table 2. For both enantiomers, plasma warfarin concentrations tended to be somewhat lower at all time points in the presence of ketorolac.

Maximum plasma warfarin concentrations (C_{max})

For both enantiomers, the maximum plasma warfarin concentrations tended to be lower in the presence of ketorolac, and this was statistically significant ($P = 0.026$) for the (S) enantiomer and almost significant ($P = 0.054$) for the (R) enantiomer by the crossover analysis. There was no evidence of a carryover effect, but the period effect was significant or almost significant with a tendency to lower C_{max} values in the second period.

Table 2 Average pharmacokinetic parameters defining the disposition of (R)- and (S)-warfarin following the administration of 25 mg of racemic warfarin to 10 healthy male volunteers in the absence and presence of chronic ketorolac administration

Parameter	Placebo		Ketorolac		Statistics	
	(R)	(S)	(R)	(S)	(R)	(S)
Maximum plasma concentration ($C_{\max}$; $\text{mg l}^{-1} \pm \text{s.d.}$)	0.95 ± 0.35	0.83 ± 0.15	0.68 ± 0.17	0.68 ± 0.14	$P = 0.054$	$P = 0.026$
Time to reach $C_{\max}$ ($t_{\max}$; $\text{h} \pm \text{s.d.}$)	2.02 ± 1.11	2.38 ± 2.05	2.21 ± 2.12	1.61 ± 0.61	NS	NS
Terminal half-life ($t_{1/2}$; $\text{h} \pm \text{s.d.}$)	39.1 ± 9.12	29.5 ± 9.36	39.6 ± 7.70	29.4 ± 10.2	NS	NS
Apparent total clearance (CL/F ; $\text{l h}^{-1} \pm \text{s.d.}$)	0.34 ± 0.08	0.50 ± 0.17	0.37 ± 0.09	0.58 ± 0.21	NS	NS
Apparent volume of distribution (V_z/F ; $\text{l} \pm \text{s.d.}$)	17.7 ± 3.49	19.2 ± 3.36	20.2 ± 2.88	22.7 ± 7.23	$P = 0.008$	NS
Fraction not bound to plasma proteins (f_u ; $\pm \text{s.d.}$)	0.0160		0.0167		$P = 0.061$	

NS = Not significant

Figure 2 Average plasma concentration-time profiles of a) (R)- and b) (S)-warfarin following the administration of a single 25 mg oral dose of racemic warfarin to healthy male volunteers in the absence (placebo; ●) and presence (○) of chronic ketorolac administration.*Time to maximum plasma warfarin concentration ($t_{\max}$)*

For both enantiomers, there were no significant differences either for treatment, period or carry-over effects. Mean maxima ranged between 1.3 and 3.1 h.

Warfarin apparent total clearance (CL/F)

There were no significant differences for either enantiomer for treatment, period or carryover effects.

Warfarin apparent volume of distribution (V_z/F)

(R)-warfarin showed a larger V_z/F value in the presence of ketorolac. This difference approached statistical significance in the first period analysis ($P = 0.065$), and was statistically significant ($P = 0.008$) in the crossover analysis. Although there was no evidence of carryover effect, there was a significant period effect in that all values were higher in the second period irrespective of treatment.

Changes of a similar direction and magnitude occurred with the (S) enantiomer, but the variance was much greater and none of the differences achieved statistical significance.

Warfarin terminal half-life ($t_{1/2}$)

The only observed statistically significant difference with this parameter was for period effect with (R)-warfarin, where second period values were higher irrespective of treatment.

Fraction of warfarin not bound to plasma proteins

At both time points, the values tended to be marginally higher in the presence of ketorolac, but no statistically significant differences were seen.

Discussion

This study aimed to look at the effects of ketorolac on the pharmacodynamic actions and pharmacokinetic parameters of warfarin. In neither case were clinically significant effects shown. For several parameters, particularly those used to assess haematological effects, significant period and carryover effects were observed. The basis of these observations is uncertain, as it is difficult to reconcile the observations with methodology. It is believed, however, that the magnitude of these effects was not sufficient to mask underlying drug effects.

Warfarin produced the expected increases in prothrombin time, Factor VII clotting time, and kaolin cephalin clotting time. Treatment with ketorolac did not significantly change the magnitude of any of these effects. Template bleeding time was increased by ketorolac relative to placebo by a factor of 1.35, which is similar to the findings of other studies. Template bleeding time is the only available gross clinical index of bleeding tendency. Ketorolac has been shown to be 37 times as active as aspirin in inhibiting the aggregation of human platelets induced by collagen and 28 times more potent than aspirin in inhibiting arachidonic acid induced aggregation. The effects of ketorolac on platelet aggregation are the basis of its effects on template bleeding time. There was no effect of warfarin treatment on the bleeding time, as expected, and no evidence of any interaction between warfarin and ketorolac.

Neither warfarin nor ketorolac, alone or in combination, affected plasma beta-thromboglobulin concentrations, suggesting that platelet consumption was not increased by any of the treatments.

Warfarin is administered as a racemic mixture, but (S)-warfarin is about five times more potent

than the (R) enantiomer in terms of anticoagulant effect in man. Alterations in the pharmacokinetic parameters of the (S) isomer are thus of considerably more clinical importance than for the (R) and are more sensitive indicators of a potential interaction than when the plasma concentration of warfarin is reported in terms of racemic drug. The pharmacokinetic parameters defining the disposition of the individual warfarin enantiomers in the placebo phase, were in agreement with those reported previously (Toon *et al.*, 1986, 1987). Ketorolac did not alter significantly the terminal half-life, apparent volume of distribution, or the oral clearance of either (S)- or (R)-warfarin.

Control values of the unbound fraction of warfarin were at the high end of literature values (Yacobi & Levy, 1977). The radiochemical purity of the [^{14}C]-warfarin (Amersham) was quoted as between 98% and 99%. A 1–2% radiolabelled impurity could result in a higher than anticipated f_u value if the impurity resided within the plasma water. If this is the case, then the f_u values are conservative estimates. A specific stereoselective method of analysing unbound warfarin concentrations would be desirable (Toon & Trager, 1984). Unfortunately, the present h.p.l.c. assay is not sufficiently sensitive to measure these concentrations.

Because of limitations in the measurement of the plasma binding of warfarin, it is difficult to make definitive quantitative statements regarding changes in the plasma protein binding of warfarin in the presence of ketorolac, other than that ketorolac displaces warfarin from plasma proteins. Obviously large changes in protein binding of a low clearance drug such as warfarin would result in correspondingly large changes in the pharmacokinetics of the warfarin enantiomers. However, such changes were not observed.

Conclusion

Ketorolac had little effect on the pharmacodynamics or pharmacokinetics of warfarin in this acute single dose warfarin study. Such studies have shown a good ability to predict clinically significant interactions between highly protein bound acidic drugs like phenylbutazone or sulphinpyrazone and warfarin (Banfield *et al.*, 1983; Toon *et al.*, 1986). The present results suggest therefore that any such interaction with ketorolac is unlikely to be of major clinical importance. However, idiosyncratic responses occur with warfarin alone, the numbers in this study were small, the subjects were carefully

selected healthy volunteers, and clinically both ketorolac and warfarin are given according to multiple-dosing regimens. Concomitant use of

ketorolac and warfarin in patients should be undertaken with due caution and appropriate monitoring.

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