Interaction between paracetamol and warfarin in patients: a double-blind, placebo-controlled, randomized study

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Background and Objectives. Paracetamol (acetaminophen) has occasionally been reported to interact with warfarin. The primary end-point of this study was to investigate whether paracetamol initiation potentiates the anticoagulant effect of warfarin and the mechanism of the interaction.

Design and Methods. In a double-blind placebo-controlled, randomized, cross-over study, 20 patients on stable oral anticoagulant therapy with warfarin for at least 1 month were randomized to receive placebo or paracetamol 1g four times daily for 14 days. International Normalized Ratio (INR) and clotting factors activities were measured before the first administration and then on days 2, 4, 7, 9, 11,14.

Results. Mean INR rose rapidly after the start of paracetamol and was significantly increased within one week of paracetamol intake compared to placebo, p=0.0002. The INR values reached a mean maximum of 3.45±0.78 with paracetamol versus 2.66±0.73 with placebo (p=0.03), corresponding to a maximum increase from baseline of 1.20±0.62 with paracetamol versus 0.37±0.48 with placebo (p<0.001). Together with the rise in INR on paracetamol treatment there were significant reductions in the vitamin K-dependent clotting factors II, VII, IX and X.

Interpretation and Conclusions. The most plausible hypothesis to explain the *in vivo* interaction is that paracetamol (or its metabolites) interfere with enzymes involved in vitamin K-dependent coagulation factor synthesis. Paracetamol at 4g daily (a dose higher than that used in clinical practice) potentiates the anticoagulant response produced by warfarin. Clinicians should be aware of this clinically significant and underestimated interaction.

Key words: paracetamol, acetaminophen, warfarin, oral anticoagulant, interaction, cross-over, randomized clinical trial.

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Warfarin, a vitamin K antagonist, is the most widely used oral anticoagulant for the prevention and treatment of venous and arterial thromboembolism and embolism related to atrial fibrillation.[1] Vitamin K antagonists act by inhibiting the vitamin K epoxide reductase, thereby reducing the activation of vitamin K-dependent coagulation factors (II, VII, IX and X).[1] The intensity of anticoagulation is assessed by measuring the International Normalized Ratio (INR).[1] Hemorrhage is the major complication of oral anticoagulants.[2,3] A strong relationship exists between the intensity of anticoagulation and the risk of hemorrhage.[1] The patient's age also appears to be an independent risk factor for the development of bleeding complications.[3-5]

Paracetamol is recommended as the analgesic and antipyretic of choice in patients on anticoagulant therapy. A combination of oral anticoagulants and paracetamol is frequently used, especially in the elderly, since indications for anticoagulation and analgesia increase with age.[6] However, recent reviews of the literature[7-9] suggest that the effect of oral anticoagulants is potentiated by concomitant paracetamol administration, although the reports are discordant. The discrepancies could be explained by some methodological weaknesses of the studies (design, evaluation criteria, study population). No prospective studies have yet evaluated the effect of paracetamol on the gold standard parameter, INR, in patients on warfarin therapy, and there are no clear-cut conclusions or clear recommendations to offer clinicians. The preliminary data of a double-blind, placebo-controlled, randomized study suggest that the introduction of paracetamol given at the maximum recommended dose (4 g/day) in patients under normal clinical conditions resulted in a significant increase in the INR.[10] The aims of the current study were to assess the overall effect of any interaction between paracetamol and warfarin on the INR and to investigate the mechanism responsible for this interaction.

Design and Methods

Aim

The main objective of this study was to assess the effect of the introduction of paracetamol on the INR in patients receiving a stable regimen of warfarin. Secondary objectives were to investigate the mechanism responsible for the interaction between paracetamol and warfarin by assessing the effect of paracetamol on vitamin K-dependent clotting factor activities and on platelet aggregation, to evaluate a correlation between INR variations and paracetamol intake, to determine a minimal duration of paracetamol administration which does not cause significant INR variations, and to identify early variations in clotting factor activities that could predict further INR changes.

Patients

Twenty outpatients of both sexes aged over 18 years were recruited in the Internal Medicine Department (Lariboisière Hospital, Paris, France) between January and October 2003. The target INR range was between 2 and 3. Patients were included if they had been on stable anticoagulation. Patients had to have been taking 2 to 9 mg a day of warfarin (Coumadine™, Bristol-Myers Squibb Company, USA) for more than one month. They were only selected if they had no recent or ongoing diseases. The intake of concomitant treatments as well as medications known to affect INR values was allowed on condition that dosages were kept constant throughout the trial. The protocol was approved by the Research Ethics Committee of La Pitié-Salpétrière, Paris, France. Each patient gave written informed consent to participation in the study after receiving oral and written information on its purposes and procedure.

Study design

This prospective, single-center study was conducted according to a double-blind, placebo-controlled, randomized and cross-over design with two treatment periods separated by a 2-week wash-out. Throughout the study, each patient had to receive the same warfarin regimen at the same hour. Patients participated in a run-in phase to verify the stability of anticoagulant treatment on the same warfarin dosage and without paracetamol co-ingestion. Patients were randomized to receive either placebo or 4g/day paracetamol (500 mg capsules, Doliprane®, Theraplix Groupe Aventis Pharma, France) in a cross-over sequence. They were included in each period provided that the anticoagulant effect was stable in the preceding 2 weeks. Placebo and paracetamol capsules were identical in appearance and were administered orally four times daily for 14 days. Randomization was performed by the Hospital Pharmacy using a random-number list with blocks of four. A physical examination was carried out and blood samples taken at the hospital on day 0 before the first study medication intake, and then at the patient's home on days 2, 4, 7, 9, 11 and 14 of each period. At every visit, patients were examined for signs of hemorrhage and thrombosis, as well as intercurrent diseases. The investigator systematically asked patients about possible lapses from the protocol such as changing any over-the-counter or prescription drugs. Each patient's compliance was assessed by counting the returned empty blister packs and the unused paracetamol and placebo capsules. Alcohol consumption and dietary intake of foods containing vitamin K were also evaluated. When patients required analgesic treatment, tramadol hydrochloride was administered at a stable dosage.

Anticoagulation management

The stability of the anticoagulation was defined by obtaining two consecutive INR in the target range on the same dosage of warfarin,[11] in the 2 weeks before inclusion. Given the long half-life and the long anticoagulant effect of warfarin,[1,11] the two INR values had to be determined at least 5 days apart and at least 8 days after any change in the dose of warfarin. If the INR remained outside the target range during the wash-out period, the warfarin regimen was readjusted and the patient entered the second study period after stabilization on the new dose.

INR and clotting factor activity measurements

The effect of paracetamol on the anticoagulant effect of warfarin was assessed by prothrombin time measurements, reported as the INR.[1,11] INR determinations were performed using two techniques: with 1.8 thromboplastin, as in routine practice, and then with 1.2 thromboplastin, which is considered to be the reference test. Coagulation factor II, V, VII, IX and X activities were determined to evaluate the effect of paracetamol on vitamin K-dependent coagulation factors. Both the INR and clotting factor activities were measured on a STA® analyser. All assays were performed in the same laboratory (Hematology-Lariboisiere Hospital, Paris, France). Peripheral blood samples of 5 mL (collected into trisodium citrate, 0.129 M) were taken on day 0 before the first intake of the study treatment, and on days 2, 4, 7, 9, 11 and 14, at approximately the same time (12 hours) after warfarin intake. Platelet-poor plasma obtained by double centrifugation (10 min at 3000 rpm, 15°C, and 12 min at 7000 rpm, 12°C) was aliquoted within 3 hours of blood collection and then frozen (-80°C). The INR was routinely measured using Neoplastin® CI, ISI 1.8 (Diagnostica Stago, France). After completion of the study, all parameters were analyzed using a single batch of reagent: the INR was measured using Neoplastin CI plus, ISI 1.2 (Diagnostica Stago, France), and clotting factor activities using specific factor-deficient plasma (FIIc, FVc, FVIIc, FIX or FX deficient plasma, Diagnostica Stago, France).

In vitro bleeding time

The effect of paracetamol on primary hemostasis was evaluated by measuring *in vitro* closure time, which is the time measured in seconds from the beginning of the test until the formation of an occluding platelet plug. Platelet adhesion and aggregation functions were assessed with a Platelet Function Analyzer PFA-100™ (Dade-Behring, Switzerland), using specific aggregation inducers [(collagen-epinephrine (EPI) and collagen-adenosine (ADP) cartridges; Dade-Behring, Switzerland)]. The effect of paracetamol on platelet function was assessed on days 0 and 14, on whole peripheral blood samples (collected into 3.8 mL tubes containing 0.38 mL of 0.129 M buffered trisodium citrate – pH 5.5).

Assessment criteria

To assess the occurrence of an interaction between paracetamol and warfarin, the primary end-point was the change in INR from baseline (ΔINR), which was analyzed by the area under the INR changes-time curve ($AUC_{\Delta INR}$) from day 0 to day 14. This criterion allows intra-individual variation to be taken into account. The $AUC_{\Delta INR}$ over the study period was calculated using the linear trapezoidal method. For each study period, in order to reduce the intra-individual variability of INR, the baseline INR value was taken as the geometric mean of the last three INR values determined before the first intake of the study treatment, on the same dosage of warfarin. Secondary end-points were the area under the clotting factor changes-time curve from day 0 to day 14 for analysis of the effect of paracetamol on clotting factor II, V, VII, IX and X activities ($AUC_{\Delta FII}$, $AUC_{\Delta FV}$, $AUC_{\Delta FVII}$ and $AUC_{\Delta FX}$, respectively), the variations of the *in vitro* bleeding time and the occurrence of hemorrhagic events.

Sample size and statistical analysis

As no data about the $AUC_{\Delta INR}$ are available in the literature, variability of INR was considered for calculating the sample size. An intra-individual variability of 0.3 INR was observed in previous studies in patients on oral anticoagulant therapy with a target INR between 2 and 3.[12] Thus, we considered that an increase in INR greater than 0.5 was significant and related to an interaction between paracetamol and warfarin. In order to show a change of 0.5 units or more in INR during the paracetamol period, we planned to include 20 patients with an α level of 5% and a power of 80%. Analyses were performed on an intention-to-treat basis. Differences in the $AUC_{\Delta INR}$ and in the areas under the clotting factor changes-time curve following administration of placebo and paracetamol were analyzed using a within-subject design ANOVA, including factors for group, treatment, period and group-by-period interactions. Analysis of the INR-time curve and INR variations at each time-point, as well as analysis of clotting factor-time curves and clotting factor variations at each time-point, were analyzed using the same design (within-subject ANOVA). The time to occurrence of a significant INR variation after paracetamol initiation was defined as the first time-point with a statistically significant INR increase. An interim analysis was scheduled after ten inclusions in order to determine whether there was a major interaction between warfarin and paracetamol and whether ethically the study should be continued.[10] Results are expressed as mean values±SD. Values of $p<0.025$ were considered statistically significant. All statistical analyses were performed using the SAS statistical software package v8.2 (SAS Institute, Cary, USA).

Safety

Safety was monitored by recording any adverse events, and by monitoring routine hematology and biochemistry parameters on days 0 and 14, including aspartate and alanine transaminases (AST and ALT), hemoglobin, blood cell counts, albumin, blood ionogram, and complementary hemostasis parameters [(activated partial thromboplastin time (aPTT)], fibrinogen and platelets).

During each study period, patients were maintained on the same dose of warfarin, even if INR values were outside the 2-3 target range. Nevertheless, in the interests of the patients' safety, the protocol specified that study treatment should be stopped if two successive INR values were over 3.5, since the higher the INR, the greater the hemorrhagic risk. In this event, warfarin was to be discontinued then restarted at the same dose as before, and the INR monitored until it returned to the target range.

Results

Patients

Twenty ambulatory patients with a mean age of 62±19 years (range 24-89 years) were enrolled and 19 (10 women and 9 men) completed the study. One patient withdrew her consent for personal reasons after 4 days in the first period and had no INR determinations, and a serious protocol deviation was observed in another patient. Both these patients were excluded from the final analysis. The baseline characteristics of the study population are listed in Table 1. Ten patients were on anticoagulant therapy to prevent thromboembolism related to atrial fibrillation, eight patients to treat pulmonary embolism and two to treat deep venous thrombosis. Patients had been receiving warfarin for a mean duration of 6.9±6.3 months.

Out of the 20 patients who were included in the study, ten received placebo first, while the other ten received paracetamol first. The wash-out period

Table 1. Baseline demographic characteristics of the population (n=20).

Characteristics	*Population (n=20)*
Age (years)	62.67±19.09 [24-89]
Gender (n female/male, %)	11/9 (55%/45%)
Body weight (kg)	76.2±18.4
Body mass index (kg/m^2)	27.2±6.7
Mean duration of warfarin therapy before inclusion (months)	6.9±6.3
Mean dosage of warfarin (mg/day)	
during placebo period	3.76±1.79
during paracetamol period	4.12±2.04
Indication for anticoagulation (n, %)	
deep venous thrombosis (without pulmonary embolism)	2 (10%)
pulmonary embolism (± deep venous thrombosis)	8 (40%)
atrial fibrillation	10 (50%)

Per protocol population is the population used for the cross-over analysis, and is defined as patients having at least one INR determination on days 0 and 14 of each period. Patients 2, 4, 9 and 12 were not included in the per protocol analysis: they completed the study but stopped the paracetamol or placebo before day 14, because of two consecutive INR values greater than 3.5. Values are presented as arithmetic mean ± SD.

Table 2. INR changes between baseline (d_0) and end of the treatment period (d_{14}).

	Paracetamol n=18	*Placebo n=18*
Mean INR peak	3.45±0.78	2.66±0.73
Mean maximum INR increase	1.20±0.62	0.37±0.48
INR (ISI 1.8)		
INR d_0	2.25±0.33	2.31±0.31
INR d_{14}	2.85±0.60	2.05±0.57
Variation INR d_0-d_{14}	0.63±0.65*	-0.24±0.55
AUC-INR$_{d0\text{-}d14}$	6.64±5.28*	-1.02±3.22
Frozen INR (ISI 1.2)		
INR d_0	2.25±0.33	2.29±0.41
INR d_{14}	2.82±0.62	2.03±0.60
Variation INR d_0-d_{14}	0.66±0.63*	- 0.23±0.55
AUC-INR d_0-d_{14}	6.63±4.64*	-1.04±3.26
Number of patients (n, %) with		
INR >4.0	5 (28%)	1 (6%)
INR >3.5	7 (39%)	1 (6%)
INR >3.0	10 (56%)	1 (6%)
INR increase >1.0	10 (56%)	1 (6%)
INR increase >0.5	17 (94%)	5 (28%)

INR: International Normalized Ratio. Values are presented as arithmetic mean ± SD. INR increase is the difference between peak and baseline INR
**p<0.001 comparison between paracetamol and placebo groups (Student's t-test).*

between the two study periods lasted 32±32 days after the first placebo period and 32±28 days after the first paracetamol period. All concomitant medications known to interact with oral anticoagulant therapy were kept constant throughout the study. The mean warfarin dosages were not statistically different between the paracetamol (4.10±2.00 mg/day) and placebo periods (3.80±2.0 mg/day). The daily doses of warfarin were identical during the two periods of treatment in 14 patients while dose adjustments were required in five patients during the wash-out because of sustained INR values outside the therapeutic range: in three patients, the doses of warfarin were increased by 0.5, 1 and 2 mg/day after the first placebo period and had to be decreased by 0.5 and 1 mg/day after the first paracetamol period.

Clinical outcome

No bleeding events were observed after either paracetamol or placebo administration. As provided for in the protocol, the paracetamol regimen was stopped early in four patients because of increases in two consecutive INR values from the 2-3 target range to 4.82 on day 4, and 3.63, 4.06 and 5.16 on day 9. Placebo administration was also stopped early in one of these patients, on day 11 (INR: 4.8). In these patients, INR values returned to the 2-3 target range within 2 to 6 days after omitting one or two warfarin doses. The reason for the high INR values in the last patient during the placebo period remains unclear. No risk factor (intercurrent pathologies, diet or change in therapy) could be found to explain the high INR during placebo administration, but an unknown concomitant disease or genetic enzymatic disorder might have played a role. One patient had a serious non-drug-related adverse event (hospitalization for a sinoatrial block) and discontinued the trial on day 4 of the second period.

Effect of paracetamol administration on mean INR

The mean AUC$_{\Delta INR}$, which was the primary end-point, was significantly higher during the paracetamol period (6.64±5.28) than during the placebo period (-1.02±3.22), p<0.001 (Table 2). This result is due to a significant rise in the INR throughout the 14-day period of paracetamol administration. In order to adjust the increase of INR (around + 40%) to the dose of warfarin (+7%), the primary end-point was analyzed taking into consideration the mean daily dose of warfarin as a co-variable. The variance analysis of mean AUC INR taking into account the dose of warfarin received in each period and INR at baseline demonstrated that the effect of paracetamol remained highly significant (p=0.0014). The effects of paracetamol on INR variations are shown in Table 2. Neither a period effect nor an order effect was found for any of the parameters, allowing complete analysis for the entire cross-over period. Table 2 shows the changes observed in INR from baseline after the initiation of placebo and paracetamol therapy. Baseline INR values before paracetamol and placebo intake were not statistically different (2.25±0.33 vs 2.31±0.31 respectively; p=0.77). No significant variations in INR were observed during the placebo period. On paracetamol therapy, a significant rise in mean INR was observed within 2 days (+0.25±0.31 on paracetamol vs 0.00±0.207 on placebo;

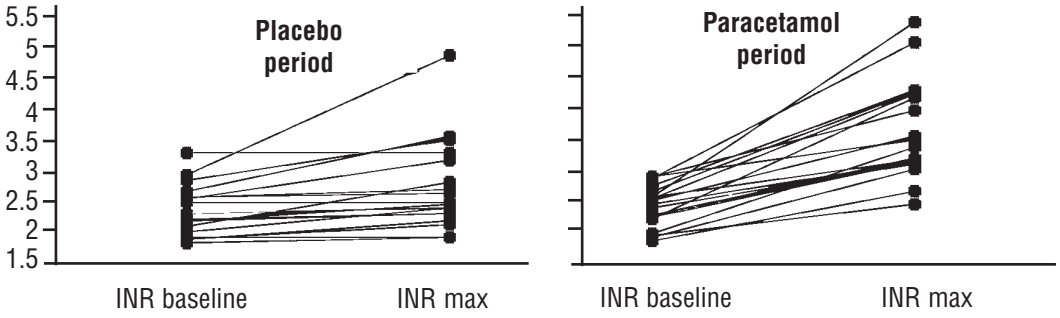

Figure 1. Individual INR data according to the allocated treatment.

p=0.007). The INR continued to increase until day 7 (0.66±0.35 vs -0.03±0.35; p<0.001) and remained significantly enhanced until the end of the treatment period. A clinically relevant INR increase (above 0.50 units) was observed 4 days after starting paracetamol. Very similar results were observed throughout the study with both thromboplastins (1.8 and 1.2) used to measure the INR (Table 2).

Effect of paracetamol administration on individual INR

Regarding maximum INR values reached in each patient, the mean INR peak was significantly higher in the paracetamol period (3.45±0.78) than in the placebo period (2.66±0.73), (p=0.03). The maximum increase on paracetamol was 1.20±0.62 whereas that during placebo administration was 0.37±0.48 (p<0.001). Figure 1 shows the individual baseline and maximum INR values observed during the two periods. Out of 18 patients, all patients except one had an INR increase greater than 0.50 units during the paracetamol period, whereas only three patients on placebo had such an increase. INR values were higher than 3.5 in seven out of 18 patients on paracetamol, compared with one out of 18 on placebo.

Effect of paracetamol administration on clotting factor parameters

Simultaneous changes in clotting factors are shown in Table 3. Baseline values before the two treatments were not different. The mean absolute AUC of factor II, VII and X changes from baseline over time were significantly greater during the paracetamol period than during the placebo period while there was no significant variation in factor V levels, suggesting a significant reduction in these vitamin K-sensitive factors throughout the 2-week paracetamol period (Table 3).

Effect of paracetamol on other parameters of hemostasis

Variations in EPI-closure time were not different between the paracetamol and placebo periods (+7.14± 21.74 sec vs +7.79±23.72 sec; p=0.62). Likewise, variations in PFA ADP-closure times did not differ between the paracetamol and placebo periods (1.43±21.61 sec vs -5.13±19.62 sec, respectively; p=0.28). The aPTT (ratio) was slightly increased in patients on paracetamol therapy whereas it was stable during the placebo period (0.16±0.21 vs -0.07±0.11, respectively, p<0.001).

Table 3. Changes in vitamin K-sensitive clotting factors (factors II, VII and X) and factor V between baseline (d_0) and the end of the treatment period (d_{14}).

Parameters	*Placebo n=18*	*Paracetamol n=18*	*p*
Factor II (%)			
FII d_0	33.18±9.61	34.44±11.65	
FII d_{14}	38.24±13.54	26.21±7.16	
FII $d_{14\text{-}d0}$	+4.47±9.36	-11.71±7.91	<0.001
AUC_{FII}	15.94±46.99	-107.20±67.97	<0.001
Factor VII (%)			
FVII d_0	46.23±13.41	44.67±10.92	
FVII d_{14}	55.06±21.59	37.43±13.59	
FVII $d_{14\text{-}d0}$	+8.18±18. 23	-7.43±13.37	0.012
AUC_{FVII}	45.44±85.35	-93.29±121.72	<0.001
Factor IX (%)			
FIX d_0	48.00±17.17	50.28±15.41	
FIX d^{14}	56.24±18.8	43.14±11.85	
FIX $d^{14\text{-}d0}$	+8.00±19.92	-9.43±14.3	0.010
AUC_{FX}	35.32±139.19	-99.46±133.07	0.011
Factor X (%)			
FX d_0	19.44± 5.55	20.56±6.96	
FX d_{14}	25.24.21±11.15	15.43±4.57	
FX $d_{14\text{-}d0}$	+5.82±10.12	-6.57±5.85	<0.001
AUC_{FX}	23.94±48.68	-65.25±56.90	<0.001
Factor V (%)			
FV d_0	101.67±20.63	96.56±22.46	
FV d_{14}	100.8±17.02	98.36±22.17	
FV $d_{14\text{-}d0}$	-0.35 ± 16.03	+1.64±16.77	0.74
AUC $_{FV}$	-3.79 ± 156.21	32.50±150.55	0.52

d_0: day 0, baseline; d_{14}: day 14; AUC: area under the curve; ΔINR, ΔF=mean absolute changes from baseline. Factor activity is expressed as a percentage of the normal levels of activity. Values are presented as arithmetic mean ± SD. p values for within-subject ANOVA

Safety

Co-administration of paracetamol was clinically well tolerated. There was one serious non-drug-related adverse event (hospitalization for a sinoatrial block). An increase in ALT (from 22 to 81 IU/L – normal range < 50 IU/L) occurred in one patient who had concomitant diarrhea. There were no significant variations in the levels of ALT and AST during paracetamol administration as compared to during placebo administration (respectively, 1.86±14.36 vs -3.18±9.24 for ALT 4.15±19.78 vs -0.41±6.79 for AST). Hemoglobin concentration, blood cell counts, fibrinogen level and platelet counts were not affected by paracetamol administration.

Discussion

Although paracetamol is the most commonly recommended analgesic for use in patients on anticoagulant therapy, there have been recent suggestions that there is an interaction between warfarin and paracetamol. Previous studies on this issue are limited by methodological biases (study design, evaluation criteria), and resulted in no conclusion on whether such an interaction exists or not. We conducted a double-blind, placebo-controlled, randomized, cross-over study in order to investigate the effect of paracetamol initiation on the pharmacodynamics of warfarin in patients on stable anticoagulation therapy for more than 1 month. Our study demonstrates that the intake of paracetamol at a dose of 4 g/day significantly increases the anticoagulant effect of warfarin in patients on previously stable anticoagulation. Mean INR rose rapidly soon after the start of paracetamol and became significantly raised after 4 days of co-administration of paracetamol and warfarin. A mean increase in INR of 0.6 was observed within 7 days. All patients except two had significant INR increases of ≥0.50. The INR values reached a mean maximum of 3.45±0.78, corresponding to an increase of about one point. This value may have been higher since it does not take into account the INR values in patients who had to stop the study treatment because of two consecutive INR values >3.5. Our results can be extrapolated to patients on oral anticoagulants since this study was performed under normal clinical conditions. The patients were stabilized on warfarin doses ranging from 2 to 9 mg a day which are daily doses widely used in clinical practice to achieve an INR between 2 and 3.[1,11] These findings have implications for everyday practice. Many studies have shown that the risk of hemorrhage is closely related to the intensity of anticoagulation: it is significantly enhanced when the INR is over 3 and increases exponentially thereafter.[13] Our results demonstrate that paracetamol intake, in the absence of any monitoring, may enhance the risk of bleeding associated with warfarin. No hemorrhagic event was reported during this study. We considered this risk to be clinically relevant in patients with at least one INR measurement over 3.5 (7/18) after paracetamol initiation; the risk was even higher in five out of 18 patients with INR values over 4. Despite the lack of a pharmacokinetic evaluation, we have shown the possibility of a pharmacodynamic interaction since the introduction of paracetamol resulted in a significant increase in INR. A persuasive explanation for the observed over-anticoagulation is a possible inhibition of the enzymes of the vitamin K-cycle by a toxic metabolite of paracetamol. In our patients, paracetamol was associated with significant reductions in clotting factor II, VII and X activities, without hepatic dysfunction (normal liver function tests and normal factor V levels). The most affected factor was factor VII (in terms of rapidity and intensity of variations), presumably because of its short half-life. The time courses of these reductions were consistent with the half-lives of the factors (VII, IX, X and finally II). These data are supported by the results of a recent *in vitro* study[12] which showed that NAPQI (a toxic metabolite of paracetamol) is an inhibitor of enzymes involved in the synthesis of the vitamin K-dependent clotting factors (vitamin K-dependent γ-carboxylase and vitamin K epoxide reductase). The unresolved issue remains the relationship between *in vitro* effects and *in vivo* observations. Whether there is an interaction between paracetamol and the other drugs of the coumarin pharmacological class remains unknown. Given the mechanism of the interaction, it is reasonable to assume that paracetamol at high daily doses also affects other coumarins.

Limitations of our study

The lack of plasma assays of warfarin and paracetamol could be criticized, but our study was conducted under normal clinical conditions, with blood taken at the patient's home, so the delay was too long for the conservation of pharmacokinetic samples. In addition, plasma R and S warfarin dosages are not available in France. We demonstrated the occurrence of an interaction but we did not assess the clinical effect of lower doses of paracetamol often used in clinical practice.

Conclusion

Since both paracetamol and oral anticoagulants are increasingly used in clinical practice, even small risks of interaction have considerable clinical and public health implications. We have demonstrated that paracetamol potentiates the anticoagulant effect of warfarin in patients on stable anticoagulant therapy without underlying diseases. Full dose paracetamol (4g/day) increases the INR by about one point, leading to an increased risk of warfarin-associated hemorrhage. Lower doses should be considered. As paracetamol is still the safest analgesic to use in combination with oral anticoagulants, we recommend early and more frequent monitoring of INR

for several weeks whenever paracetamol (as well as any other drug) is added or withdrawn from the regimen of a patient treated with an oral anticoagulant. Our results support the hypothesis that paracetamol (or its metabolites) interfere *in vivo* with enzymes involved in vitamin K-dependent coagulation factor synthesis.

IM: substantial contributions to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be published; NB: contributions to acquisition of data, analysis and interpretation of data, drafting the article; LD: substantial contributions to the conception and design of the study, and interpretation of data, revising it critically for important intellectual content; and final approval of the version to be published; CBDS: substantial contributions to acquisition of data, analysis of data; GS: substantial contributions to analysis of data; EM: substantial contributions acquisition of data, or analysis of data; CC: final approval of the version to be published; JFB: substantial contributions to design of the study, analysis and interpretation of data, revising the manuscript critically for important intellectual content; and final approval of the version to be published. The authors declare that they have no potential conflict of interest.

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