REVIEW ARTICLE

Drug Safety 2004; 27 (5): 325-333
0114-5916/04/0005-0325/$31.00/0

Does Paracetamol Potentiate the Effects of Oral Anticoagulants?

A Literature Review

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Contents

Abstract

Paracetamol (acetaminophen) is the analgesic and antipyretic therapy of choice for patients receiving oral anticoagulation. It is widely used by patients in both prescription and over-the-counter products, resulting in frequent co-prescription with oral anticoagulants, especially in elderly patients. Indeed, older patients are the most likely to receive this combination of drugs because indications for both oral anticoagulation and analgesic therapy increase with age.

For many years reports have presented evidence both for and against the idea that paracetamol may potentiate the anticoagulant effect of oral anticoagulants, thus increasing haemorrhagic risk in patients receiving this combination of drugs. This issue has continued to be a matter of debate in recent publications. No clear practical conclusion can be drawn from the studies because of methodological bias and the lack of clinical relevance. No prospective, randomised study assessing the effect of paracetamol on the anticoagulant effect of oral anticoagulants as used in clinical practice (i.e. the types of patients and dosages used in clinical practice) are available in the literature. The implications are considerable since on the one hand, the ingestion of paracetamol may be a cause of altered anticoagulation in patients who regularly take oral anticoagulation and who may have a haemorrhagic risk factor; and on the other hand, paracetamol might be the analgesic drug of choice that can be used without the need for any restrictions in patients receiving oral anticoagulant drugs. A comprehensive search of Medline and EMBASE for studies and case reports from 1966–2002 was performed in

order to review the available literature on the interaction between paracetamol and oral anticoagulant drugs.

In conclusion, the potential interaction between oral anticoagulant drugs and paracetamol is an important unanswered question, due to the growing incidence of the concomitant use of these drugs and the possible bleeding implications. The association between paracetamol and the occurrence of excessive INR values remains controversial due to lack of prospective clinical studies assessing the effect of the prescription of paracetamol in patients receiving long-term oral anticoagulation in clinical conditions. Such a study is currently ongoing.

Oral anticoagulation is highly effective in treating and preventing thromboembolism. The major complication is the occurrence of bleeding.[1] Some risk factors that predispose patients to bleeding have been identified, such as the intensity of the anticoagulant effect (assessed by the International Normalized Ratio [INR]), the length of therapy and the concomitant use of drugs that interfere with oral anticoagulation.[1,2] In particular, the risk for intracranial haemorrhage, the most feared complication of anticoagulation, increases dramatically at an INR of >4.[3]

Elderly patients are the most prone to receive concomitant oral anticoagulant and analgesic therapy. Indeed, the incidence of medical conditions requiring oral anticoagulation and analgesic therapy both increase with age. The incidence of indications for oral anticoagulation increase with age (venous thromboembolism, atrial fibrillation) as well as conditions causing pain (the most frequent in the elderly are cancer and rheumatoid diseases).[4] Therefore, the choice of the analgesic drug is of critical importance in this population.

Aspirin (acetylsalicylic acid) and NSAIDs enhance the risk of bleeding associated with oral anticoagulants by inhibiting platelet function; and they can also produce gastric erosions that increase the risk of upper gastrointestinal bleeding.[1,2]

Cyclo-oxygenase (COX)-2 inhibitors are a new alternative therapy to NSAIDs in those patients who have pain due primarily to associated inflammatory states. They seem to be an attractive alternative analgesic therapy since they selectively inhibit COX-2, with anti-inflammatory and analgesic properties; they allow COX-1 activity to remain intact, having no effect on platelet aggregation and bleeding time compared with placebo and cause less gastropathy than NSAIDs.[5] No significant difference in prothrombin times (PT) was observed in 24 healthy volunteers on stable doses of warfarin who were randomised to receive either celecoxib 200mg twice daily or placebo for 7 days.[4] In a cross-over study carried out in 27 patients, the effect of three dosages of rofecoxib (12.5, 25 and 50 mg/day on the anticoagulant effect of a single dose of warfarin was assessed: an 8% increase in INR was observed with the combination of warfarin plus rofecoxib 25 mg/day, but there were no clinical implications.[6]

Nevertheless, COX-2 inhibitors can not be recommended as first-line analgesic therapy in elderly patients receiving oral anticoagulation since bleeding events and increases in INR have been reported in patients receiving concomitant oral anticoagulation and COX-2 inhibitors (rofecoxib and celecoxib), especially the elderly.[7-9] The US FDA has requested a change in the product labelling for celecoxib and rofecoxib: it must now include a precaution about monitoring anticoagulant activity, particularly during the first few days after initiating or changing celecoxib therapy, in patients receiving warfarin.[10,11]

Paracetamol (acetaminophen) is currently the analgesic and antipyretic therapy of choice for patients receiving oral anticoagulation.

In the US, paracetamol is the most frequently ingested medication.[12] It is widely used by patients in both prescription and over-the-counter products, resulting in frequent co-prescription of paracetamol and oral anticoagulants.

Some reports suggest that even modest amounts of paracetamol can potentiate the anticoagulant effect of oral anticoagulants, thus increasing the haemorrhagic risk in patients receiving both drugs.[12] The ingestion of paracetamol may be an under-recognised and common cause of altered anticoagulation in patients who regularly take oral anticoagulation.[13]

A comprehensive search of Medline and EMBASE for studies and case reports from 1966–2002 was carried out in order to review the available literature on the interaction between oral anticoagulants and paracetamol. The trials needed to address one or more of the following items: analgesic, paracetamol, oral anticoagulation, bleeding, INR. All methodological schemes were considered for inclusion in this review.

The primary objective of the study is to assess the data for and against the occurrence of a potentiation of the anticoagulant effect of oral anticoagulation with paracetamol in clinical conditions, according to the level of evidence provided by the trial in question.

1. Studies of Concomitant Use of Oral Anticoagulants and Paracetamol (Acetaminophen)

The hypothesis that paracetamol potentiates the anticoagulant effect of oral anticoagulants has been a matter for debate for 30 years.[14,15] Conflicting data have been reported in studies with widely variable methodologies and clinical relevance (from observational and retrospective studies to case reports, experimental studies in healthy subjects and *in vitro* models). However, as yet no prospective randomised trial assessing the influence of paracetamol on the anticoagulant effect of oral anticoagulants in clinical conditions has been published.

Basically, observational studies in patients have revealed a dose-dependent enhancement of the anticoagulant effect of oral anticoagulants (most often warfarin) by paracetamol while pharmacodynamic studies in healthy subjects have not.

Reports available in the literature will be reviewed for each oral anticoagulant drug, from high to low levels of evidence related to the design and the methodology of the study. The methodological characteristics of the trials, the number of subjects and the dosage used for each study are presented in table I.

1.1 Studies Conducted with Warfarin

Hylek et al.[13] conducted a prospective case-control study in an anticoagulation therapy unit in order to identify factors associated with an INR >6 in case patients and appropriate control subjects (mean age was 70 years) who had been administered warfarin for >1 month, whose target INR was 2–3.[13] The 93 case patients had an INR >6 (range 6.1–29.8) and the 196 controls had an INR between 1.7–3.3. Case and controls patients did not differ in terms of age, sex, race, indication for anticoagulation therapy, length of warfarin therapy, dosage of warfarin or INR value preceding the study period. Fifty-two cases (56%) and 70 controls (36%) reported taking paracetamol in the week preceding the study INR. There was a dose-dependent relationship between the intake of >7 paracetamol tablets per week and an increased risk for an INR >6 (the adjusted relative odds [OR] was 3.5 [95% CI 1.2, 10] for intake of 2275mg to 4549mg paracetamol per week and 6.9 [95% CI 2.2, 21.9] for 4550mg to 9099mg per week). For patients who reported taking the equivalent of at least 4 regular-strength (325mg) paracetamol tablets per day for >1 week, the odds of having an INR >6 were increased 10-fold above those taking no paracetamol (95% CI 2.6, 37.9). Other risk factors independently associated with an elevated INR were advanced malignancy, taking new drugs known to potentiate warfarin, taking more warfarin than prescribed, decreased oral intake and diarrhoea.

In a prospective, double-blind, cross-over study, 15 healthy male volunteers receiving a stable dose of warfarin with a target prothrombin time (PT) ratio of 1.35–1.5 were randomised to receive 2 weeks each of paracetamol 4 g/day or placebo. Significant elevation of the PT was observed (>1.75 times the ratio in 7 of 15 subjects compared with 1 in the placebo group; >20% from baseline, p = 0.02). The

Table I. Characteristics of studies investigating the effect of paracetamol (acetaminophen) on oral anticoagulation. The trials are presented according to the oral anticoagulant drug used and the level of evidence presented by the trial

	Oral anticoagulation	Methodology	Paracetamol dosage (mg)	Duration of the association	No. of subjects	Evaluation criteria	Results
Hylek et al.[13]	W for more than 1mo, INR 2–3	Prospective, case-control	325 – ≥1.3 g/day (mean: 6.7 g/wk)	1–4 wks	93 pts; 196 controls	INR	Odds for INR >6 ↑10-fold for ≥9.1 g/wk
Rubin et al.[16]	W, stable dose; PT ratio 1.35–1.5	Prospective, randomised double-blind	4 g/day	2 wks	15 healthy volunteers	PT	↑20% (7 of 15 pts); ↑2 times the control (5 of 15 pts)
Udall[17]	W, stable dose for at least 2 wks	Prospective, patient own-control	3.25 g/day	2 wks	10 healthy volunteers	PT	No difference
Kwan et al.[18]	W, single dose of 20mg	Pharmacokinetic, prospective	4 g/day	1 day and 2 wks	20 healthy volunteers	PT, factor VII	No difference
Fattinger et al.[19]	P, stable dose	Prospective, case-control	2.22 g/day	5 days	54 pts; 180 controls	INR, daily dose	No difference; phenprocoumon dose lower with paracetamol (3.2mg vs 3.6mg, p = 0.077)
Boeijinga et al.[20]	C	Prospective, randomised, double-blind	500mg q4d	3 wks	20 healthy volunteers	Thrombotest	↑14% by wk 1
Antlitz et al.[14]	W, A, C, P	Prospective, randomised, double-blind cross-over	650mg q4d	4 wks	12 pts; 50 controls	PT	↑5.3 sec by wk 3
			650mg q4d	2 wks	50 pts/controls (cross-over)	PT	↑3.6 sec by wk 2
Anlitz and Awalt[15]	P, W	Prospective, randomised, double-blind	650mg; 2 dosages given 4h apart	1 day	20 healthy volunteers	PT	No difference

A = anisidione; **C** = coumarin; **INR** = International Normalised Ratio; **P** = phenprocoumon; **PT** = prothrombin time; **pts** = patient; **q4d** = four times daily; **sec** = seconds; **W** = warfarin; ↑ = increase.

potentiating effect was detected after 7 days of paracetamol intake and peaked at 12.5 days.[16]

In a prospective study, ten healthy subjects with stable warfarin dosages for at least 2 weeks were given paracetamol 3.25 g/day for 2 weeks and served as their own pre-treatment controls. No difference in PT was observed.[17]

The effect of a pretreatment with paracetamol on the anticoagulant response to a single-dose of warfarin 20mg was studied in a pharmacokinetic drug-interaction study performed in 20 healthy volunteers. On three occasions, volunteers were given a single-dose of warfarin 20 mg: alone, after 1 day of paracetamol 4 g/day, and after 2 weeks of paracetamol 4 g/day. The pharmacodynamic response to a single dose of warfarin, assessed by PT and factor VII concentration up to 96 hours remained unchanged irrespective of the intake of paracetamol.[18]

Three case reports reporting an interaction between warfarin and paracetamol have been published: one case of haematuria and gingival bleeding on warfarin with enhanced PT,[21] one case of retroperitoneal haematoma (with increased INR) on warfarin[22] and one case of an abrupt increase of INR after taking paracetamol in a patient on warfarin, which occurred again after reintroduction of paracetamol, with a concomitant decrease of factor VII level.[23]

1.2 Studies Conducted with Phenprocoumon

Phenprocoumon is widely used in some countries of continental Europe. In the only study of the effect of paracetamol on the action of this agent, phenprocoumon-treated patients with at least one INR determination in at least 4 days were consecutively divided into two groups according to the use, or not, of at least 1300 mg/day paracetamol in the 3 days preceding the INR determination.[19] The patients in the paracetamol group (n = 54; mean age 65 years) received paracetamol 2220 ± 651 mg/day on average, and the median duration of exposure was 5 days; the comparison group contained patients without paracetamol exposure during a hospital stay (n = 180; mean age 64 years). No significant difference in INR values between the 2 groups (0.3, 95% CI 0.6, 0.1) was observed, while the mean daily phenprocoumon dose was slightly lower in the paracetamol comparison group (3.2mg versus 3.6mg, $p = 0.077$). There was no significant dose-dependent interaction of paracetamol on the anticoagulant effect of phenprocoumon ($p = 0.2$), at a dosage of 222 ± 651 mg/day for 3 days.[19]

1.3 Studies Conducted with Coumarin

In a prospective, double-blind, parallel, placebo-controlled study randomising 20 volunteers taking coumarin to receive paracetamol 500mg four times daily or placebo for 3 weeks, a significant increase in 'thrombotest' times of 14% occurred within 1 week of administration of paracetamol ($p < 0.05$) compared with subjects receiving placebo.[20]

1.4 Studies Conducted with Acenocoumarol

One case has demonstrated potentiation of the effect of acenocoumarol by concomittant paracetamol. The patient had a stable INR (average 2.46) on acenocoumarol 2 mg/day and paracetamol 1–2 g/day. Thirteen days after stopping paracetamol the INR decreased to 1.62, and 1.67 after another week. One week after paracetamol 1 g/day was restarted the INR was 2.02 and a week later it was 2.01.[24]

1.5 Studies Conducted with Several Oral Anticoagulants

In a prospective double-blind placebo-controlled study, 112 patients on stable doses of oral anticoagulation (warfarin, anisindione, coumarin, phenprocoumon) were assigned to the following regimen: 50 subjects served as controls and continued on anti-coagulation only; 12 received paracetamol for 4 weeks (650mg four times/day), and 50 received the same dosage of paracetamol or placebo for 2 weeks in a cross-over fashion.[14] Patients receiving warfarin and paracetamol for 4 weeks had a significant increase in PT of 5.3 seconds by week 3 ($p = 0.05$) compared with the control period and patients in the cross-over groups experienced an increase in PT of 3.6 seconds by week 2 ($p < 0.05$) compared with the control 2 weeks.

In a prospective, double-blind, placebo-controlled study of 20 subjects, two doses of paracetamol 650mg given 4 hours apart given to ten of the patients receiving stable dosages of oral phenprocoumon and sodium warfarin did not interfere with the PT or with the anticoagulant effect of warfarin.[15]

Most of the above studies were carried out in patients on warfarin therapy who were given paracetamol 2 to 3.2 g/day concomitantly for periods of 2 to 3 weeks. The effect of paracetamol on the anticoagulant effects of other oral anticoagulant drugs has been evaluated less frequently. The existence of an interaction between paracetamol and the whole coumarin pharmacological class is possible[25] but can not be established with available reports because of the lack of methodological relevance. So, possible mechanisms have been suggested to account for the interaction.

2. Physiopathological Hypotheses for a Potential Interaction Between Oral Anticoagulants and Paracetamol

Whyte et al.[26] observed that paracetamol may increase INR: they studied patients who were admitted to a regional toxicology treatment centre with paracetamol poisoning and with INR measurements and without potentially confounding co-ingestion or hepatic injury. Exposed and non-exposed (control) cohorts were recruited from admissions with paracetamol and psychotropic drug poisoning, respectively. After exclusions, there were 143 admissions and 205 estimations of INR. Retrospective analysis showed that 50% of all patients and 66% of those with an extrapolated 4-hour paracetamol concentration >150 mg/L had an abnormal INR at some time. INR showed a time- and dose-dependent increase. In the prospective part of the study, which involved 30 exposed patients and eight controls, INR was significantly higher in exposed patients than in controls (1.36 versus 1.17; $p = 0.004$); functional factor VII was also lower in exposed patients than in controls (58% versus 110%; $p = 0.003$). Factor IX was also lower ($p = 0.02$). This small rise in INR after paracetamol poisoning without hepatic injury may be caused by the inhibition of vitamin K-dependent activation of coagulation factors (by inhibiting gamma carboxylation). But this study does not reflect clinical conditions since the median paracetamol dosage was 20g, which is much higher than the usual therapeutic dosage. So, the hypothetical mechanism cannot be extrapolated to clinical situations.

Both warfarin and paracetamol undergo hepatic metabolism and are metabolised to various degrees by cytochrome P450 (CYP) 1A2 and CYP3A4. The mechanism by which the anticoagulant effect of warfarin (and other oral anticoagulants) may be potentiated by paracetamol is unclear.

Commercially available warfarin is a racemic mixture of *R*- and *S*-enantiomers. *S*-warfarin is much more potent and is predominantly metabolised to 7-hydroxywarfarin by CYP2C9 and to a smaller extent by CYP3A4 whereas *R*-warfarin is metabolised by CYP1A2, CYP2C19, and CYP3A4.[27] The normal metabolism of warfarin, which occurs via hepatic CYP, is a complex mechanism that can be competitively and noncompetitively inhibited by many medications.

At therapeutic dosages, paracetamol is metabolised by CYP1A2, CYP2E1, and CYP3A4.[27-29] In addition, paracetamol may be an unrecognised but clinically significant inhibitor of CYP3A4[30] (based on observations from *in vitro* experiments). Since paracetamol is neither a substrate nor an inhibitor of CYP2C9, the predominant route for the metabolism of warfarin, the findings of a striking, dose-dependent increase of anticoagulant effect by paracetamol is subject to caution.

Several potential explanations have been forwarded,[31] without a clear conclusion.

First, CYP2C9 exhibits polymorphisms affecting warfarin administration (in up to 25% of Caucasians).[19] Certain alleles cause an individual to become a poor metaboliser of warfarin, which may shift the metabolism of *S*-warfarin towards CYP3A4 and therefore increase the significance of metabolic interferences involving CYP3A4. Secondly, paracetamol may competitively inhibit metabolism of *R*-warfarin by one or both isoenzymes, thus prolong-

ing the serum half-life of *R*-warfarin. Thirdly, the discrepant observations in the literature regarding the clinical significance of the interaction may depend on the clinical conditions of the subjects.[27] With ageing, there is a decrease in CYP2E1 activity; paracetamol might be metabolised preferentially by CYP1A2, and CYP3A4 over CYP2E1.[32] Otherwise, conditions predisposing to tissue hypoxia or arterial hypertension may result in increasing the metabolism of paracetamol by CYP2E1, CYP1A2 and CYP3A4.[33-37]

Clinically inconsistent reports or studies about the potentiation of the anticoagulant effect of oral anticoagulation by paracetamol continue to be regularly published, without clear conclusion and clear recommendation for the clinician. This paradoxical situation can be explained by the lack of prospective randomised trials assessing the effect of the introduction of paracetamol on the anticoagulant effect of each oral anticoagulant drug.

3. Methodological Limitations of the Studies

Differences in study design are a possible explanation for the divergent results from previous studies. If a drug interaction occurs only in a so-far-as-yet unidentified small subgroup of susceptible individuals, a case-control design would preferentially include susceptible individuals among the cases and not the controls and thus detect a difference, whereas only a few susceptible individuals would be included in a cohort study and thus no difference would be detected.[19]

Case-control studies must address concerns about bias. The primary concern of selection bias is minimised by nesting the case-control study with a known population.[13] However, this method is susceptible to more bias than randomised controlled trials or cohort studies.[38]

In addition, it is difficult to draw definitive conclusions based on data obtained in retrospective study; the possibility of another undefined confounding factor can not be overlooked. The fact is that there is the potential for pharmacodynamic interactions because dose-response relationships are determined in controlled study conditions and are affected by both pharmacokinetic and pharmacodynamic variables. This review should be considered an exploratory review of the subject.

In clinical studies, the evidence for the presence or absence of an interaction was assessed using variable criteria (INR, PT, Factor VII), which makes comparisons between studies very difficult and hazardous. Studies performed in healthy volunteers do not represent patients with visceral impairments and polypharmacy. *In vitro* studies are only indicative and try to provide an explanation for the mechanism of the interaction but they are far from clinical conditions and do not take into account *in vivo* concentrations, therapeutic interferences and hepatic polymorphisms.

Finally, prospective cross-over studies performed in patients on warfarin and receiving full-dose paracetamol (4g daily) are not available. We have undertaken such a study, which is ongoing.

4. Recommendations and Conclusions

The question of an interaction between paracetamol and the anticoagulant effect of oral anticoagulant drugs is of importance in clinical practice and may have implications for therapy since these medications are often used concomitantly, especially in the elderly. The occurrence of an interaction may have direct practical implications for the clinician and the patient since the bleeding risk induced by oral anticoagulants drugs may be increased.

The question of whether there is a potentiation of effect by paracetamol on oral anticoagulant drugs remains unanswered. If such an effect exists, the second remaining question is the size of this interaction, which may vary individually and according to the timing of administration: prolonged use of paracetamol increases the effect of warfarin but even a short course of paracetamol-containing compounds can lead to a rapid rise in the INR.[39] In the case report by Bell,[25] the administration of paracetamol to a patient who had been receiving a stable dose of warfarin was found to increase the INR within 18 to 48 hours, while Kwan et al.[18] and others concluded that brief exposure to paracetamol

for patients receiving stable dosages of warfarin is safe, but they did not address the effect of prolonged exposure. Results can not be extrapolated to patients taking long-term, high-dose paracetamol.[40]

In order to conclude if paracetamol exerts a significant influence on the anticoagulant effect of warfarin or not (and if it does, on the size and the dose-dependence of the effect), we are conducting a randomised trial assessing the effect of paracetamol for 14 days on INR in patients receiving a stable dose of oral anticoagulation with a target INR between 2–3. Practical conclusions for the clinician will be drawn.

While waiting for these results, since paracetamol does not inhibit platelet function and cause gastrointestinal bleeding, it is still much safer to use than aspirin and other NSAIDs for patients taking warfarin.[1,2] Because of a lack of a safer alternative and a definitive response to all the questions, if a patient being treated with an oral anticoagulant drug requires an analgesic or antipyretic drug, paracetamol should still be the drug of choice but the dose and duration of therapy should be as low as possible and monitored carefully (<1.3 g/day for 2 weeks if possible).[26,31]

In any case, it is recommended that the anticoagulant effect of oral anticoagulant drugs be closely monitored in the case of paracetamol co-administration. In France, the health authorities recommend monitoring INR twice weekly during concomitant treatment with oral anticoagulants and paracetamol. Indeed, the anticoagulant response is individual (the reduction in coagulation factors and increase in INR did not occur in all patients) and there is a relatively narrow therapeutic window (target INR of between 2–3).[1,2] In addition, there are many drug-drug interactions with oral anticoagulant therapy: medications can prevent, alter, or enhance the activity of oral anticoagulation.[1,2]

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the contents of this review.

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