

What affects anticoagulation control in patients taking warfarin?

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ABSTRACT

Background

The ageing population is taking an increasing number of both prescribed and non-prescribed medication. Little is known of the potential for adverse drug reactions between these. Warfarin is a commonly prescribed medication, well known for its potential to cause serious adverse reactions in combination with many prescription medicines. It has been suggested that herbal medicines such as garlic, either as a dietary supplement or in cooking, may also interact with warfarin, resulting in poor international normalised ratio (INR) control.

Aim

To determine whether, for patients who take garlic as well as warfarin, the proportion of the INR tests in range is lower than in comparable patients who do not take garlic.

Design of the study

Retrospective study of patients taking prescribed warfarin.

Setting

Primary care practices in Somerset and Devon.

Method

Three controls (not taking garlic) matched for age, sex, and general practice were compared with each patient self-reporting taking garlic as a supplement. INR results were assessed for the preceding 12 months. Potentially confounding factors were considered, for example diabetes mellitus; all prescribed medication; any bleeding episodes.

Results

No evidence was found to suggest that garlic consumption either as a supplement or in cooking is associated with more frequent haemorrhagic complications or less control of INR. Poor INR control may, however, be associated with taking larger numbers of prescription medicines, particularly during prescription changes.

Conclusion

Further research would be warranted into whether increased INR monitoring is needed when drug changes are made. These data render clinically significant interactions between warfarin and garlic intake unlikely.

Keywords

anticoagulation; complementary medicine; garlic; prescriptions; warfarin.

INTRODUCTION

The ageing population is taking an increasing number of medications of all types: prescription,¹ over-the-counter (OTC),² complementary, and alternative.³⁻⁵ Warfarin is a commonly prescribed medication which is well known for its potential to cause serious adverse drug reactions, namely bleeding,^{6,7-9} especially as a result of many prescription medications interacting with it. In addition, some herbal preparations may interact with it as well. However, there is a widely-held public belief that, because many of the non-prescription medications are 'natural' remedies, they can do no harm.¹⁰ Unfortunately, many can cause adverse effects,¹¹ just as traditional prescription medication can.⁶ Of particular concern is the possibility of such herbal preparations interacting with prescription medicines;¹² increasing the risk of an adverse reaction or altering the pharmacodynamics of the prescribed drug.

One common herbal preparation is garlic. Patients usually take it for the prevention of cardiovascular disease, and a recent review concluded that it is superior to placebo in reducing total cholesterol levels, even though the size of the effect is of debatable clinical relevance.¹³ Garlic is also cited as potentiating the effect of warfarin, and affecting the

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Submitted: 22 July 2008; Editor's response: 17 September 2008; final acceptance: 11 March 2009.

©British Journal of General Practice

This article was originally online first on 15 July 2009. Cite this article as: *Br J Gen Pract* 2009; 59: 590-594. Advance online publication. DOI: 10.3399/bjgp09X453800

international normalised ratio (INR),^{12,14} although the evidence presented in review articles appears to be limited to anecdote and occasional case reports.^{15–17} It is uncertain whether increased bleeding times, if a real effect, are due to reduced platelet function,^{18–21} or prolonged prothrombin or partial thromboplastin times.²²

When undertaking a prevalence study in the south west of England,⁴ the authors found that in a population of 1360 patients on long-term warfarin, approximately 100 (7%) were taking garlic as well as warfarin. The study did not investigate the control of INR in relation to garlic ingestion, and therefore this retrospective study was conducted to test whether INR control is jeopardised if patients take garlic and/or other prescription medicines.

The present study aimed to answer the question: for patients who take garlic as a dietary supplement as well as warfarin, is the proportion of their INR tests in range lower than in comparable patients who do not take garlic? Secondary objectives were: to assess the effects of prescription medicines and garlic (as a supplement or in cooking)⁷ on INR control, and the number of major bleeding episodes and disease complications.

METHOD

In the autumn of 2005, all general medical practices in Somerset and Devon that participated in the original WHIST (Warfarin Herb Interaction Study) study⁴ were invited by letter to take part in this second study. Each participating practice was paid between £50 and £200, depending on list size, to cover their administrative costs. Approvals were obtained from both the Somerset and Devon Ethics Committees and primary care trusts. It is standard practice in these two counties for patients on warfarin to be monitored solely by their GP, who receives INR results and then advises the patient on any dose changes that may be required and the time interval until their next INR test. A few practices test the INR within the practice (near-patient testing), and a small minority of patients are managed by secondary care.

Those practices that agreed to take part searched their electronic patient databases to identify all patients who were taking warfarin, and sent them an invitation letter, information sheet, consent form, freepost envelope, and questionnaire. This questionnaire was based on that used in the previous study (available on request).⁴ Two weeks later, a short reminder was sent by practices to all patients who were sent the original mailing. Replies were returned to the central research office. Practices were excluded if they did not use electronic patient records. Patients were excluded if: they had been taking warfarin for less than 3 months, were terminally ill, <18 years of age, unable to read

How this fits in

For some patients prescribed warfarin, it proves difficult to maintain blood coagulation levels within the range required. A number of possible contributory factors have been suggested for this, including the use of garlic as a dietary supplement or in cooking. In this retrospective study of 1130 patients, it was found that interaction with other prescription medicines, particularly those newly prescribed, was of greater significance than the ingestion of garlic.

English, or unable to understand the consent form (for example, those with dementia). Participating practices were responsible for excluding these patients from their mailing lists.

Three controls (not taking garlic) were compared with each patient self-reporting taking garlic as a supplement. The returned questionnaires were used to identify those patients taking garlic supplements. For each such patient, the three controls that most closely matched were selected from those patients on warfarin who had reported not taking garlic. Controls were matched on age (within 3 years), sex, and general practice.^{6,7,23,24} The signed consent form gave permission for the researchers to review patients' primary care medical records. Two research assistants visited participating practices and searched the patients' GP electronic records for the 12 months prior to the consent date, without being aware of which patients had been taking garlic: a standard proforma was used for extraction. All INR results with dates were noted, as well as a number of potentially confounding diagnoses, for example diabetes mellitus, all prescribed medication, and any bleeding episodes. Patient questionnaires were relied upon to record herbal intake of garlic and frequency of use in cooking.

The primary outcome measure was the proportion of INR tests in the target range within the 12-month period prior to the signed consent date; it was assumed that the index INR applied to the whole time period back to the previous INR result. Secondary outcome measures were: the percentage of time INR was within the target range, average number of INR tests undertaken in previous year, and incidence of bleeding side-effects.

Based on a systematic review,²⁵ it was expected that approximately 60% of INR test results would be within the target range. To detect a 10% change in this figure with a power of 80% and $P = 0.05$, the study would need 75 patients taking garlic and 225 controls. With the planned size as above it would have been possible to detect a change of 20% in adverse effects.

Useable replies were entered onto a database and SPSS was used for analysis. Descriptive data are presented summarising the outcome measures within the two groups of patients. Planned independent

Table 1. Characteristics of those 216 patients taking or not taking garlic as a dietary supplement.

	Total	Taking garlic as a dietary supplement		P-value
		Yes (n = 54)	No (n = 162)	
Age, ^a years; mean (SD)	71.5 (8.4)	71.9	71.4	
Male sex	144	36	108	1.00
Any other supplement	83	41	42	<0.001
Any OTC medication	32	5	27	0.13
Diabetes	25	3	51	0.14
Reason for taking warfarin:				
Atrial fibrillation	136	39	97	0.11
Previous stroke	21	5	16	0.56
Previous DVT or embolus	48	13	35	0.72
Heart valve replacement	23	4	19	0.37
Heart failure	11	2	9	0.45
Duration of use, years; median (IQR) ^b	5.0 (2–9)	5 (2–9)	5 (2–8.25)	0.69
Percentage of INR tests, ^c median (IQR)				
Below target INR range	17 (5–28)	15 (7–31)	17 (1–27)	0.99
Within target INR range	67 (50–80)	69 (52–82)	65 (49–79)	0.24
Above target INR range	13 (7–23)	12 (0–23)	14 (8–23)	0.35

DVT = deep vein thrombosis. IQR = interquartile range. OTC = over the counter. SD = standard deviation. All results are Pearson χ^2 test, except ^aStudent's *t*-test. ^bMann-Whitney *U* test.

variables included reason for taking warfarin, duration of warfarin treatment, presence or absence of co-ingestion of garlic in cooking, age, co-ingestion or not of other medication known to affect INR and/or blood clotting, and diabetes mellitus. Associations were tested using either Student's *t*-test, Pearson's χ^2 , Mann-Whitney *U* test, or Spearman's ρ . Prescribed medication was classified as potentiating (definitely or possibly), no effect, or inhibiting (possibly or definitely) the effect of warfarin on the INR according to the *British National Formulary*.²⁶

RESULTS

Of 87 practices invited, 21 took part. These practices identified 1790 eligible patients, of whom 1130 (63%) returned consent forms and questionnaires. Fifty-four patients reported taking garlic as a dietary supplement: 39 took it daily, nine most days, and five weekly (one not known); they had taken it for variable durations (<1 year, *n* = 7; 1–4 years, *n* = 14; 5–9 years,

n = 10; ≥10 years, *n* = 21 (not known, *n* = 2). Of 205 patients, 39 never used garlic in cooking, 99 used it occasionally, 41 weekly, 20 on most days, and six used it daily (11 not known). Those taking garlic supplements were more likely to use garlic regularly in cooking (*P* < 0.001) and to take other supplements (*P* < 0.001; Table 1). No significant differences were found for other important variables (Table 1).

Patients were taking a wide range of prescribed medication. It was noted for each of these whether the patient had taken it continuously for the 12 months prior to consent, taken it intermittently, for example an antibiotic, stopped it having taken it as a regular repeat, or started it as a regular repeat, for example a blood pressure-lowering tablet (Table 2).

Thirty-two patients suffered abnormal bleeding (28 rectal bleeding, three subconjunctival haemorrhage, and one extensive skin bruising); the incidence of abnormal bleeding was similar between the two groups (9.3% of the 54 taking garlic supplements

Table 2. Number of different prescribed medications per patient (excluding warfarin) classified by type of use over the 12 months of the study; and absolute number of patients given any medication that is known to interact with warfarin.

Type of use	Median number of drugs taken by 214 patients (IQR; range)	Number of patients taking at least one drug in each category that:			
		Increased INR		Decreased INR	
		Definitely	Possibly	Definitely	Possibly
Continuously taken	3 (1–5; 0–12)	54	54	14	0
Started taking during the year	0 (0–2; 0–10)	24	13	4	0
Taken intermittently	1 (0–2; 0–8)	30	49	1	0
Stopped taking during the year	0 (0–1; 0–6)	10	10	1	1

IQR = interquartile range.

versus 16.7% of the 162 not; $P = 0.13$). Excluding those on garlic supplements and warfarin for <1 year made no difference (results not shown). Bleeding was not related to garlic in cooking ($P = 0.92$).

The median (interquartile range [IQR]) number of days in the previous 12 months when the INR results were low, in the target range, or high were 27 (3–70), 285 (210–323) and 20 (3–46) respectively. The median (IQR) number of occasions when the INR results were low, in the target range, or high were 2 (1–5), 9 (7–11), and 2 (1–3) respectively.

Thirteen patients suffered thrombotic episodes (10 deep vein thrombosis, one pulmonary embolus, one transient ischaemic attack, and one stroke). These events were not associated with either taking garlic supplements (5.6% of 54 versus 6.2% of 162; Fisher's exact test $P = 1.00$) or garlic in food (Mann–Whitney U test, $P = 0.73$).

Use of garlic and OTC medication and INR control

Taking garlic as a dietary supplement was not associated with deterioration of INR control. The median (IQR) number of INR tests within the target range was 65% (49–79%) for those not taking garlic supplements and 69% (52–82%) in those taking them (Mann–Whitney U test $P = 0.24$). Excluding those patients not taking warfarin and/or those not taking garlic for at least 1 year did not affect these results ($P = 0.27$). Garlic supplementation was not significantly associated with the median percentage of tests either higher or lower than the target range (Table 1). Garlic in cooking was not significantly correlated with the percentage of tests above, below, or within the target INR range ($\rho = 0.11$, $P = 0.12$; $\rho = -0.08$, $P = 0.29$; $\rho = -0.02$; $P = 0.75$ respectively). The taking of any OTC medication was not significantly associated with INR control (results not shown).

Prescription medication and INR control

Many patients were given drugs that are known to interact with warfarin (Table 2). The percentage of INR test results in the normal range was negatively associated with the number of new drugs started within the year ($\rho = -0.15$, $P = 0.042$), but not associated with the number of repeat drugs stopped during the year ($\rho = -0.02$, $P = 0.82$), the number of drugs used intermittently ($\rho = -0.03$, $P = 0.74$), or the number taken continuously ($\rho = 0.12$, $P = 0.10$). However, the percentage of test results below the target INR range was significantly associated with the number of drugs taken continuously ($\rho = -0.17$, $P = 0.041$) and the number of new repeat drugs started ($\rho = 0.29$, $P < 0.001$). No significant associations were found with the number of INR results above the target range (all P values > 0.20).

Medical conditions and INR control

The percentage of INR tests in the target range was significantly associated with patients having a heart valve replacement (Mann–Whitney U test, $P = 0.006$; median [IQR] = 48.7% [32.0–75.3%] with heart valve replacement versus 67.4% (56.0–80.0%) without heart valve replacement) but not with patients experiencing atrial fibrillation, heart failure, prior cerebrovascular accident, prior thrombosis, or ongoing diabetes mellitus (results not shown). However, the percentage number of tests below the target range was associated with heart valve replacement ($P = 0.039$; 18.5% (3.4–28.6%) heart valve replacement versus 6.2% (0–17.6%) no heart valve replacement), heart failure ($P = 0.025$; 1.1% [0–8.1%] with heart failure versus 8.8% [1.9–20.9%]), and with atrial fibrillation ($P = 0.027$; 12.0% (0–25.0%) with atrial fibrillation versus 20.0% (7.7–28.8%) without atrial fibrillation).

DISCUSSION

Summary of main findings and limitations of the study

No evidence was found to suggest that garlic consumed either as a supplement or as a foodstuff is associated with more frequent haemorrhagic complications or less control of INR. However, it was found that many patients on warfarin are being prescribed medication by their GP, that can affect INR control. In particular, poor INR control appears to be associated with taking larger numbers of prescription medicines, particularly during prescription changes. These findings are consistent with several scenarios. First, garlic might not interact with warfarin in a clinically relevant fashion. This is not an unlikely possibility as the documentation of such an interaction is based on less than convincing data. Second, the present study might have failed to detect a true interaction. Obviously observational data are plagued by a host of confounders, and also the size of this study might have been too small to detect a true difference in those taking garlic.

Comparison with existing literature

It is known that poor INR control is associated with antibiotic prescription and newly prescribed potentiating medication.^{7,9} The present study found that around a quarter of patients experienced such prescription medication changes during the study year. Such changes may well affect INR control and lead to either bleeding complications or complications of the disease for which the warfarin is prescribed. The study finding that poor INR control is associated with larger numbers of prescription medicines is consistent with published studies.^{6,27} However, it was found that INR results were more likely to be below the target INR range, reducing the chance of bleeding complications;

this may be because GPs were advising patients to reduce their warfarin dose because they were aware of the potential for interaction. Clearly, however, lowering of the INR would put patients at higher risk of complications of their disease process, for example thrombosis.

The ageing population is taking increasing numbers of drugs.¹ This could lead to compliance problems. In the absence of certainty, it can be argued that patients and their professional carers should be cautious about the possibility of interactions between herbal or prescription medicines and warfarin. Patients only rarely discuss their non-prescription medicines with their GPs,⁴ and underestimate the risks of both prescribed²⁸ and herbal medication.⁴ The new GP contract puts a clear responsibility upon GPs to regularly review patients and to ensure that treatments are based on sound evidence.¹ This has led to more prescriptions being issued; adverse drug reactions are associated with both age and the total number of types of drug being taken.⁶ There are effective ways of educating patients about their medication.²⁹ The authors suggest that this should include an enquiry about herbal medicine use, particularly with those at high risk, such as older people and those taking warfarin.³⁰ Where control of INR is poor, it is expected that GPs would explore whether herbal medications or other OTC preparations that might affect the INR are being taken.¹⁷

Implications for clinical practice and future research

The authors argue that the effect of prescription changes warrants further exploration, as the prevalence of interaction is around the same level as for herbal and complementary medicine self-medication.⁴ There may well be certain clinical scenarios when such discussion will become mandatory in the future, such as certain diseases, for example diabetes, malignancy,^{6,7,23} and certain genetic variants,³¹ or when INR control is difficult to achieve. Further research would be warranted into the potential for interactions between any oral therapy and warfarin in terms of adverse effects, advice to patients, and whether increased INR monitoring is needed when drug changes are made.

Funding body

The Rufford Maurice Laing Foundation (reference 10522)

Ethics committee

Somerset REC (04/Q2202/47)

Competing interests

The authors have stated that there are none

Acknowledgements

We would like to thank all practices who distributed questionnaire packs to their patients, and all patients who returned study documentation allowing access to their notes.

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REFERENCES

1. British Medical Association. *Quality and Outcomes Framework guidance*. London: BMA, 2008.
2. British Medical Association. *Over-the counter medication*. London: BMA, 2005.
3. Ernst E, White AR. The BBC survey of complementary medicine use in the UK. *Complement Ther Med* 2000; **8**(1): 32–36.
4. Smith LFF, E Ernst, P Ewings, et al. Co-ingestion of herbal medicines and warfarin. *Br J Gen Pract* 2004; **54**(503): 439–441.
5. Ross S, Simpson C, McLay JS. Homeopathic and herbal prescribing in Scotland. *Br J Clin Pharmacol* 2006; **62**(6): 647–652.
6. Wiffen P, Gill M, Edwards J, Moore A. Adverse drug reactions in hospital patients. *Bandolier Extra* 2002; **June**: 1–16.
7. Hylek EM, Heiman H, Skates SJ, et al. Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA* 1998; **279**(9): 657–662.
8. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005; **165**(10): 1095–1096.
9. Glasheen JJ, Fugit RV, Prochazka MD. The risk of over-anticoagulation with anticoagulants in outpatients on stable warfarin regimens. *J Gen Intern Med* 2005; **20**(7): 653–656.
10. Ernst E, Pittler MH, Wider B, et al. *The desktop guide to complementary and alternative medicine*. 2nd edn. Edinburgh: Elsevier Mosby, 2006.
11. Ernst E, Pittler M, Wider B, et al. *Oxford handbook of complementary medicine*. Oxford: Oxford University Press, 2008.
12. Miller LG. Herbal medicines: selected clinical considerations focussing on known or potential drug-herb interactions. *Arch Intern Med* 1998; **158**(20): 2200–2211.
13. Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolaemia. A meta-analysis of randomised clinical trials. *Ann Intern Med* 2000; **133**(6): 420–429.
14. Sunter W. Warfarin and garlic. *Pharmacology* 1991; **246**: 722.
15. Vaes LPJ, Chyka PA. Interactions of warfarin with garlic, ginger, ginkgo or ginseng: nature of evidence. *Ann Pharmacother* 2000; **34**(12): 1462–1478.
16. Evans V. Herbs and the brain: friend or foe? The effects of ginkgo and garlic on warfarin use. *J Neurosci Nurs* 2000; **32**(4): 229–233.
17. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs* 2001; **61**(15): 2163–2175.
18. Rose KD, Croissant PD, Parliament CF, Levin MB. Spontaneous spinal epidural haematoma with associated platelet dysfunction from excessive garlic ingestion. *Neurosurgery* 1990; **26**(5): 880–882.
19. Mar C, Bent S. Clinical evidence: an evidence based review of the 10 most commonly used herbs. *West J Med* 1999; **171**(3): 168–171.
20. Thomson M, Mustafa T, Ali M. Thromboxane B2 levels in serum of rabbits receiving a single intravenous dose of aqueous extract of garlic and onion. *Prostaglandins Leukot Essent Fatty Acids* 2000; **63**(4): 217–221.
21. Ang-Lee MK, Moss J, Yuan CS. Herbal medicines and perioperative care. *JAMA* 2001; **286**(2): 208–216.
22. Fugh-Berman A. Herb–drug interactions. *Lancet* 2000; **355**(9198): 134–138.
23. Goudie BM, Donnan PT, Fairfield G, et al. Dependency rather than old age increases the risk of warfarin-related bleeding. *Br J Gen Pract* 2004; **54**(506): 690–692.
24. Humphries KH, Kerr CR, Connolly SJ, et al. New onset atrial fibrillation. Sex differences in presentation, treatment and outcome. *Circulation* 2001; **103**(19): 2365–2370.
25. Fitzmaurice DA, Kesteven P, Gee KM, et al. A systematic review of outcome measures reported for the therapeutic effectiveness of oral anticoagulation. *J Clin Pathol* 2003; **56**(1): 48–51.
26. *British National Formulary* 52. London: BMJ Publishing Group and RPS Publishing, 2006.
27. Archer EL, Boyle DK. Herb supplement use among the retail population of an independent, urban herb store. *J Holist Nurs* 2008; **26**(1): 27–35.
28. Cullen G, Kelly E, Murray FE. Patients' knowledge of adverse reactions due to medications. *Br J Clin Pharmacol* 2006; **62**(2): 232–236.
29. Wofford JL, Wells MD, Singh S. Best strategies for patient education about anticoagulation with warfarin: a systematic review. *BMC Health Serv Res* 2008; **8**: 40.
30. Milton JC, Hill-Smith I, Jackson SH. Prescribing for older people. *BMJ* 2008; **336**(7644): 606–609.
31. Schwarz UI, Ritchie MD, Bradford Y, et al. Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med* 2008; **358**(10): 999–1008.