the option of renal transplantation from living donors should be more widely discussed.

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Human gastric mucosal bleeding induced by low dose aspirin, but not warfarin

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Abstract

Objective—To investigate the suitability of treatment with low dose aspirin or warfarin, or both, as possible prophylaxis against cardiovascular disease by determining the effect on gastric mucosal bleeding.

Design—Randomised crossover trial.

Setting—Academic department of therapeutics.

Subjects—Twenty healthy male volunteers aged 19-22.

Interventions—On separate occasions and in randomised order all subjects received aspirin 75 mg, warfarin, or aspirin 75 mg combined with warfarin. Each treatment was given for 12 days or (when warfarin was used) for longer if necessary until the international normalised ratio of the prothrombin time was stable at 1.4-1.6.

End point—Loss of blood over 10 minutes into gastric washings.

Measurements and main results—Bleeding over 10 minutes into gastric washings under baseline conditions and after five days, and at end of each regimen of treatment. Aspirin 75 mg increased bleeding from 0.60 (95% confidence interval 0.36 to 0.99) μ l/10 minutes to 1.26 (0.71 to 2.25) μ l/10 minutes at five days, with no evidence of either progressive change or adaptation thereafter. Warfarin had no effect on bleeding either alone or when combined with aspirin.

Conclusions—Aspirin 75 mg causes gastric mucosal bleeding. Low dose warfarin neither induces gastric mucosal bleeding nor enhances that caused by aspirin.

Introduction

Thrombosis is a common feature of both unstable angina and death from ischaemic heart disease and unstable angina. This may be related to enhanced

platelet activity^{1,2} or increased amounts of fibrinogen and factor VII, which have been associated with fatal and non-fatal ischaemic heart disease.³⁻⁶ The effect that aspirin has on the function of platelets has been shown to reduce morbidity and mortality in patients with unstable angina and myocardial infarction and to be probably beneficial in the primary and secondary prevention of myocardial infarction.⁷⁻²⁰ Trials have tended to use progressively lower doses of aspirin as these cause maximum inhibition of synthesis of thromboxane by platelets, have a minimal effect on synthesis of prostacyclin by vessel walls, and substantially prolong the bleeding time.²¹⁻²³ For these reasons doses of aspirin of less than 100 mg a day might theoretically be more effective than higher doses, but for the same reasons they might render patients prone to bleeding that is also seen with higher doses.⁷⁻²⁰

Anticoagulant treatment with warfarin has also been used to prevent myocardial infarction. Although it is probably beneficial,²⁴ its continued use causes a progressive increase in bleeding.²⁵ An alternative approach is to use lower doses to normalise the increased activity of factor VII found in patients prone to vascular disease,⁶ but whether this would cause less bleeding is as yet unproved.

Possibly optimum benefit would accrue from combining low doses of aspirin and warfarin, and this approach is to be investigated by the Medical Research Council in a large community based study.²⁶ Because a combination of treatments has the potential to enhance harm (particularly gastrointestinal bleeding) as much as benefit we investigated the effect of low doses of aspirin and warfarin, alone and in combination, on gastric mucosal bleeding.

Subjects and methods

Twenty healthy non-smoking male volunteers aged 19 to 22 participated in the study. They did not have a

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history of dyspepsia, easy bruising or bleeding, or intolerance to aspirin or warfarin. Normal blood counts, platelet counts, and coagulation profiles were required before the study. The subjects did not take any drugs other than those related to the trial and did not drink alcohol during the periods of treatment. The protocol was approved by Nottingham Medical School's ethical committee. All subjects gave informed written consent.

Each subject was studied under baseline conditions and during and after each of three treatments. (1) Aspirin 75 mg a day was given for 12 days. (2) Warfarin was given at an initial dose of 2 mg a day, which was adjusted according to the international normalised ratio of the prothrombin time every two to three days, and continued for at least 12 days or until the ratio was 1.4-1.6 for at least two consecutive readings. (3) Aspirin 75 mg a day and warfarin were combined. At the end of a period of monotherapy with one of these drugs the other drug was added and both drugs were continued for a further 12 days or until the international normalised ratio of the prothrombin time was 1.4-1.6 for at least two consecutive readings.

The subjects were randomised to four cohorts, which received the treatments in different orders. The figure shows two of the schedules of treatment; the other two schedules were similar, but period 1 and periods 2 and 3 were reversed. The subjects were studied after five days and at the end of each of the three periods of treatment. In addition, baseline measurements were made before dosing in 10 subjects and after the completion of treatment in the other 10. On another occasion (not randomised) subjects were given aspirin 600 mg four times a day for five days for comparison with low dose aspirin.

On each day that subjects were tested they underwent orogastric intubation with a 16 French gauge Salem sump tube (Sherwood, Belgium) two hours after they had taken the drug. Gastric juice was aspirated while the subjects rested, and the stomach was rinsed three times by the rapid introduction, dispersal, and aspiration of 100 ml distilled water. A 10 minute collection then began. After five minutes 2 mg phenol red in 15 ml distilled water was introduced and dispersed around the stomach. After nine minutes 100 ml distilled water was instilled, dispersed, and aspirated at 10 minutes. After two more rapid rinses a second 10 minute collection began, and after two further rapid rinses a third 10 minute collection was performed. Whenever water or phenol red was introduced subjects performed a standardised series of manoeuvres to ensure dispersal of the liquid within the stomach.

The volume and pH of, and concentrations of blood and phenol red in, each of the timed aspirates were measured. The pH was measured with a glass

Blood loss ($\mu\text{l}/10$ minutes) into gastric washings for 20 subjects treated with warfarin or aspirin, or both. Numbers are geometric means (95% confidence intervals)*

	Day	
	5	Final
Warfarin	0.60 (0.33 to 1.10)	0.58 (0.35 to 0.99)
Aspirin 75 mg a day	1.26 (0.71 to 2.25)	1.24 (0.56 to 2.75)
Warfarin and aspirin	1.11 (0.58 to 2.13)	0.93 (0.46 to 1.87)
Aspirin 2.4 g a day	8.38 (5.13 to 13.70)	

*Baseline blood loss 0.60 (0.36 to 0.99) $\mu\text{l}/10$ minutes.

electrode (Corning). Phenol red was measured spectrophotometrically at 560 nm after a 1/4 dilution of gastric aspirate with ammonium hydroxide.²⁷ Blood was measured by using the peroxidase activity of haemoglobin to oxidise *o*-tolidine to produce a colour reaction.^{27, 28} For this assay aliquots of gastric aspirate (0.2 ml) were mixed with 1.8 ml citrate buffer (12.6 g citrate monohydrate and 9.8 g trisodium citrate/l, pH 3.8 at room temperature) and *o*-tolidine (2 g/100 ml glacial acetic acid). Forty five seconds later 0.4 ml hydrogen peroxide (20 volumes/100 ml) was added and the solution mixed gently. The rate at which a blue-green colour developed was measured by the difference in absorbance, measured at 640 nm, 30 and 60 seconds after hydrogen peroxide was added. Samples were compared with standards prepared from the subjects' blood.

Statistical methods—Loss of gastric mucosal blood in each timed aspirate was calculated after correction for recovery of phenol red. Data from any aspirate from which less than 25% of the phenol red was recovered were rejected, and the medians of the remaining samples were used for analysis. Data on bleeding were logarithmically transformed to approximate a normal distribution. The changes in bleeding after treatment with aspirin 75 mg or warfarin, or both, from baseline values were analysed by two way factorial analysis of variance. Values for pH were assessed non-parametrically by Friedman two way analysis of variance. Other comparisons were by paired Student's *t* test. A value of $p < 0.05$ (two tailed) was regarded as significant. Based on the variance of blood loss under baseline conditions the study had the power ($\alpha = 0.05$, $1 - \beta = 0.8$) to detect a doubling in rates of mucosal bleeding to 1.2 $\mu\text{l}/10$ minutes.²⁹

Results

The subjects tolerated the treatment regimens and the study procedure well and did not experience adverse effects. One subject, however, was withdrawn from the study because of erratic attendance especially while taking warfarin. When the data from all the cohorts for each period of the different regimens were combined the mean final dose of warfarin needed to achieve an international normalised ratio of the prothrombin time in the target range of 1.4-1.6 was 4.0 (95% confidence interval 3.4 to 4.6) mg a day without aspirin and 4.0 (3.4 to 4.7) mg a day with aspirin. At the first orogastric intubation during warfarin treatment the international normalised ratio was 1.41 (1.30 to 1.52), and during treatment with warfarin combined with aspirin it was 1.49 (1.34 to 1.64). At the second intubation at 12 days or more it was 1.46 (1.41 to 1.52) and 1.50 (1.46 to 1.54) respectively. These values were achieved at 11 (interquartile range 9-13) and 16 (14-17) days respectively.

The table shows the amount of bleeding into the stomach with each of the treatments. Low doses of aspirin caused a significant increase in gastric bleeding ($p < 0.05$), but warfarin, by itself or in combination with the aspirin, had no significant effect. Although

Examples of two schedules of treatment. Each cohort contained five subjects; other two schedules were as for A and B but with periods 2 and 3 before period 1. Arrows show when subjects were studied, at days 5 and 12 or when international normalised ratio of prothrombin time stabilised

low doses of aspirin increased gastric bleeding by a factor of 1.9 (95% confidence interval 1.1 to 2.5), this was significantly less than the increase by a factor of 14 (8 to 26) caused by aspirin 2.4 g a day ($p < 0.01$) (table). There was no significant difference in the amount of bleeding at five and 12 days of any of the treatments. By the end of the periods of combined treatments 10 subjects had received aspirin for more than 24 days (with warfarin during the second half of the period (figure)). The mean value for bleeding at the end of this period was 0.53 (0.23 to 1.17) $\mu\text{l}/10$ minutes, which was not significantly different from the corresponding value of 0.60 (0.25 to 1.42) $\mu\text{l}/10$ minutes seen in the same subjects after five days of the initial monotherapy with aspirin.

Discussion

Doses of aspirin in the range we used in this study are widely believed to be harmless to the gastric mucosa. Our study showed, however, that 75 mg a day caused a significant increase in gastric mucosal bleeding. By contrast, warfarin in doses sufficient to raise the international normalised ratio of the prothrombin time by 50% did not seem to induce bleeding on its own or to enhance the bleeding seen with aspirin. An important feature of this study was that dosing continued over longer periods (up to two weeks for each treatment alone and four weeks in which combination treatment followed monotherapy) than in most other studies of acute injury due to aspirin. This allowed us to address a critical question: whether the risk of bleeding increased with time or, alternatively, whether it decreased by a process of adaptation. With high doses of aspirin and indomethacin there is evidence that mucosal injury, measured by bleeding and changes on endoscopy, is greatest in the first week of ingestion and that adaptation occurs with prolonged ingestion.³⁰⁻³² A recent report suggested that time to adaptation is dose dependent, being of two or three weeks with aspirin 650 mg twice daily and two to eight weeks with 650 mg thrice daily.³² Our study showed quite clearly that neither progressive bleeding nor adaptation occurred after five days with continued ingestion of aspirin 75 mg a day for up to one month.

An important factor in the success of any regimen of warfarin proposed for widespread use is its simplicity and safety. We used an extremely cautious regimen because there was little information available to guide the choice of dose. In practice, the final dose was 2.5-7.0 mg in all subjects and 3-5 mg in all but five of the satisfactory dosing periods. Thus initial stabilisation on 3 mg a day for one to two weeks with subsequent adjustment of the dose would take most subjects into or near the desired therapeutic range easily, rapidly, and safely.

A reasonable criticism of the present study is that we used young rather than elderly subjects. In the few studies that have compared experimental gastrointestinal bleeding from aspirin in different age groups there was no evidence that bleeding was greater in the elderly.^{33,34} As far as can be determined, therefore, our data probably apply to those older people in whom prophylaxis with aspirin and warfarin is most appropriate and risk of haematemesis and melaena is most significant,³⁵ but this can be confirmed only by direct investigation in this age group.

Taken in context with other studies we have performed on aspirin, the acute injury measured by bleeding is clearly dose dependent. The bleeding associated with 75 mg a day was some fivefold less than that associated with aspirin 1.8-2.4 g a day and about half that seen with aspirin 300 mg a day.^{26,36,37} As yet we are uncertain whether our data are relevant to long

term treatment as results from recent trials of aspirin prophylaxis for cardiovascular disease have been conflicting. In a study of aspirin 500 mg a day given to British doctors there was a significant increase in peptic ulceration (by 58%) compared with that in controls and a non-significant increase in gastrointestinal bleeding, which led to the withdrawal of 2.2% of subjects taking aspirin.¹⁷ By contrast, the brief interim report from the United States physicians' health study, in which 325 mg aspirin on alternate days was used, stated that there was little evidence of these complications.¹⁶ In a third study, on the effect of aspirin on transient ischaemic attacks, aspirin 300 mg and 1200 mg daily (pooled data) was associated with increased dyspepsia and gastrointestinal bleeding.¹⁸ Although aspirin 300 mg had a significantly lower effect than 1200 mg, it seemed to be associated with a higher incidence of bleeding than placebo, but the numbers were too small for significance to be determined.

Overall these studies suggest a dose dependent effect for aspirin given long term, which parallels the effects we have shown with short term treatment, with relatively little harm at doses below 300 mg a day. The main problem with this interpretation is that the subjects in the United States physicians' study may have been unusually healthy as their incidence of cardiovascular disease was much lower than expected; in addition, those found on screening to have aspirin intolerance were excluded before randomisation. Our study showed that doses even as low as 75 mg a day are harmful, though to a lesser extent than 300 mg a day. Although higher doses of aspirin cause low rates of acute bleeding, they lead to major problems in some patients. Our study suggested that there is also a risk of such major problems with low dose aspirin but probably at a lower rate.

When patients present with bleeding peptic ulcers two quite different mechanisms are possible. Aspirin's gastroduodenal toxicity may lead to the development of peptic ulcers, some of which bleed. Alternatively, aspirin's ability to inhibit synthesis of thromboxane, interfere with aggregation of platelets, and prolong the bleeding time²¹⁻²³ may cause silent ulcers to bleed. This remains a strong possibility as there is a significant increase in the relative risk of bleeding with short term or light aspirin consumption.^{38,39} Aspirin's antiplatelet action may have been an important factor in the bleeding we observed as doses in the range we used cause maximum inhibition of synthesis of thromboxane by platelets.^{22,23} Bleeding from sites other than the gastrointestinal tract has been associated with aspirin for up to five days after ingestion.⁴⁰ Of particular current concern is the unresolved possibility that low doses of aspirin may increase the incidence of haemorrhagic stroke.¹⁶⁻¹⁹

In contrast, although low dose aspirin causes gastric mucosal bleeding, there is no evidence that this is enhanced by concurrent use of low dose warfarin or that these doses have any effect alone. This was seen for treatment periods of up to one month, though we do not know whether this would apply to bleeding at other sites. Our data suggest that a trial of low dose aspirin combined with low doses of warfarin would carry no greater risk of gastrointestinal bleeding than that associated with low dose aspirin alone. As the risks of aspirin 75 mg daily, though measurable, are small taking this with low dose warfarin may offer the best combination of therapeutic advantage and safety, and a trial of such treatment in patients at risk of vascular disease is warranted.

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Mineralocorticoid deficiency in HIV infection

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Infection with the human immunodeficiency virus (HIV) may result in adrenal necrosis and hence a deficiency of cortisol.^{1,2} We report on a patient who developed severe sodium and water depletion because of a deficiency in production predominantly of mineralocorticoids. This important, easily treatable complication has probably been overlooked in patients infected with HIV.

Case report

A homosexual man aged 41 was admitted in April 1988 with a diagnosis of pneumocystis pneumonia. He was positive for HIV antibody. On admission his serum sodium concentration was 129 mmol/l, potassium 4.7 mmol/l, and urea 5.1 mmol/l. Treatment with high doses of co-trimoxazole was started. His symptoms improved, and he was discharged 11 days later. His serum sodium concentration, however, had fallen during his admission and at discharge was 114 mmol/l; serum potassium and urea concentrations were 5.8 mmol/l and 9.7 mmol/l, respectively. His serum cortisol concentration was measured, but the result was not available at discharge.

He was readmitted the next day complaining of feeling faint on walking, leg weakness, and breathlessness. Examination showed profound postural hypotension (blood pressure lying 120/80 mm Hg, un-

recordable on standing); hyponatraemia (sodium concentration 110 mmol/l) and hyperkalaemia (potassium concentration 6.7 mmol/l) were more pronounced. Treatment with intravenous physiological saline relieved the symptoms, and Addison's disease was diagnosed provisionally. At this stage, however, the serum cortisol concentration in the sample obtained during the first admission was found to be 992 nmol/l (normal 250-550 nmol/l). He was given oral dexamethasone (0.5 mg twice daily) and sustained release sodium 600 mg three times daily, and an intravenous tetracosactrin test was performed (table). Plasma renin activity (after 10 minutes' sitting) was appreciably raised at 55 nmol/l/h (normal 0.4-1.9 nmol/l/h), and plasma aldosterone concentration was 149 pmol/l, which was low considering his high plasma renin activity. His 24 hour urinary excretion of sodium was 240 mmol. Treatment was changed to hydrocortisone 20 mg in the morning and 10 mg at night with fludrocortisone 0.1 mg daily, which was increased to 0.2 mg daily. Within 10 days this had corrected his postural hypotension (blood pressure lying 110/70 mm Hg, standing 130/80 mm Hg) and restored his serum electrolyte concentrations to normal (sodium 136 mmol/l, potassium 3.6 mmol/l, and urea 3.3 mmol/l). Plasma renin activity fell to 5.8 nmol/l/h and plasma aldosterone concentration remained low at 59 pmol/l. He was negative for autoantibodies, and computed tomography of his adrenal glands showed a normal size and structure.

Comment

The patient's high plasma renin activity and low plasma aldosterone concentration with profound hyponatraemia indicated a severe mineralocorticoid