placebo. The reverse occurred in one patient, who had a single episode with methenamine hippurate but was otherwise free of infection. The Wilcoxon matched pairs rank sum test gave a significant result ($p<0.01$).

Out of five relapses, four occurred while patients were taking placebo. Most infections were due to *Escherichia coli* (table). There was no difference between patients taking extra fluid and those with a normal fluid intake (28 versus 24 attacks), and extra fluid did not reduce the efficacy of methenamine hippurate (six versus five attacks). There were no signs of a carryover effect, and 23 episodes occurred in the first year versus 29 in the second year.

Organisms causing acute cystitis during study

Drug treatment	Total No of cases of cystitis	No of cases during extra fluid intake	No of cases during ordinary fluid intake
Placebo	41	22	19
		(<i>E coli</i> 15, <i>Klebsiella</i> 3, <i>Proteus mirabilis</i> 3, unknown 1)	(<i>E coli</i> 11, <i>Klebsiella</i> 3, <i>Proteus mirabilis</i> 1, <i>Enterobacter</i> 1, <i>Enterococci</i> 3)
Methenamine hippurate	11	6	5
		(<i>E coli</i> 3, <i>Proteus mirabilis</i> 1, <i>Streptococcus</i> group B 1, unknown 1)	(<i>E coli</i> 5)

Discussion

We found 2.1 infections per patient/year with placebo but only 0.8 with methenamine hippurate ($p<0.01$). These figures are better than those reported after administration of 2 g methenamine mandelate together with 2 g ascorbic acid, indicating that ascorbic acid is unnecessary.

Because methenamine hippurate is well tolerated, is effective, and fails to produce cross resistance to conventional antibiotics it seems to be a suitable prophylactic agent against recurrent acute cystitis in women.

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Atrial natriuretic peptide concentrations in pre-eclampsia

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Abstract

The concentration of plasma immunoreactive atrial natriuretic peptide is positively associated with right atrial and pulmonary capillary wedge pressure, suggesting that blood volume and hence atrial pressure govern its release. Expansion of plasma volume is a central physiological adjustment in normal pregnancy. Conversely, pregnancies complicated by pre-eclampsia are associated with a reduction in plasma volume and central venous pressure. A study was therefore undertaken to test the hypothesis that plasma atrial natriuretic peptide concentrations are low in pre-eclampsia owing to deficient secretion. Concentrations of the peptide were measured by a specific radioimmunoassay.

The mean plasma immunoreactive atrial natriuretic peptide concentration in healthy pregnant women ($n=22$; third trimester) was higher (56 (1 SD 29) ng/l) than in 25 young, non-pregnant controls (37 (19) ng/l). Concentrations in patients suffering from mild pre-eclampsia ($n=9$) were higher (127 (60) ng/l) than in

normal pregnant women, and in patients with severe pre-eclampsia ($n=6$) concentrations were higher still (392 (225) ng/l).

Despite failure of plasma volume expansion and low central venous and pulmonary capillary wedge pressures in pre-eclampsia this condition is associated with greatly increased plasma concentrations of plasma immunoreactive atrial natriuretic peptide, which increase still further with the severity of the disease. These findings are clear evidence that atrial pressure may not be the principal determinant of the release of the natriuretic peptide in pre-eclampsia.

Introduction

The atria of the heart have long been thought to have a role in blood volume control. It has recently been shown that atrial natriuretic peptide is released into the blood by stretching of the atria after expansion of the blood volume. Atrial natriuretic peptide acts on the kidney to promote excretion of salt and water, thus decreasing the extracellular fluid volume and maintaining homeostasis.¹ Besides the direct natriuretic and diuretic effects atrial natriuretic peptide inhibits vasoconstriction induced by angiotensin II and noradrenaline and reduces secretion of both renin and aldosterone.²

The physiological adjustments in normal pregnancy include an increase in plasma volume, renal plasma flow, and glomerular filtration rate and a decrease in total peripheral resistance. In addition, normal pregnant women are extremely resistant to the pressor effect of infused angiotensin II.³ By contrast, in pre-eclampsia there is a failure of plasma volume expansion⁴ accompanied by salt retention. Renal plasma flow and glomerular filtration rate are less than in normal pregnancy and patients show an increased pressor responsiveness to angiotensin II⁵ and an increase in

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total peripheral resistance.⁶ Hence, given the known regulatory mechanisms and actions of atrial natriuretic peptide, we might expect to find low concentrations of plasma immunoreactive atrial natriuretic peptide in pre-eclampsia.

In an attempt to test the hypothesis that plasma immunoreactive atrial natriuretic peptide concentrations are low in patients with pre-eclampsia we have compared these values with those in normal women of the same age.

Subjects and methods

To establish a normal range of plasma immunoreactive atrial natriuretic peptide concentrations in young women blood was taken from 25 non-pregnant women (mean age 27.6 (range 19-38) years) with no history of pre-eclampsia or renal or cardiovascular disease. These women were selected at random from the technical staff at the department of clinical chemistry, Sundby Hospital. Blood samples were also drawn from 22 randomly selected normal women in the third trimester of pregnancy (mean age 29.5 (range 19-37) years) and from 15 consecutive patients (mean age 28.3 (range 21-36) years) with newly discovered pre-eclampsia. All subjects were taking their usual diet and none was receiving any kind of medication other than iron or vitamin supplements. Each patient was investigated shortly after admission. Patients were diagnosed as pre-eclamptic and classified as having mild or severe disease according to criteria of the American College of Obstetricians and Gynecologists.⁷

Atrial natriuretic peptide assay—After at least 30 minutes' rest and with the subjects supine 10-12 ml blood was taken from a peripheral vein into chilled polystyrene tubes containing inhibitors of proteolytic enzymes (disodium edetic acid, aprotinin, and soybean trypsin inhibitor). After centrifugation at 4°C each plasma sample was divided into three 0.5-2.0 ml aliquots and 1.5-6.0 ml 2.9% acetic acid added to each. Acidified plasma samples were applied to Sep-Pak C₁₈ cartridges (Waters Associates, Milford, MA, USA), which were prepared by sequential washing with 5 ml methanol and 5 ml distilled water. After being washed with 10 ml distilled water atrial natriuretic peptide was eluted with 2 ml 80% ethanol plus 4% acetic acid. The eluates were reduced to near dryness at 45°C by evaporation under nitrogen and lyophilised. Samples were then redissolved and radioimmunoassay of atrial natriuretic peptide done by using specific rabbit anti- α natriuretic polypeptide serum (Peninsula Laboratories). Iodine-125 labelled α atrial natriuretic peptide (human) was used as tracer and synthetic human α atrial natriuretic peptide (1-28) used to construct standard curves. Standards and samples were incubated for 96 hours at 4°C in a final volume of 440 μ l. Bound and free ligands were separated by adding dextran coated charcoal. All samples were extracted and assayed in triplicate. Sensitivity of the assay was 5 pg/tube. Intra-assay and interassay variations were 5.9% (n=10) and 11.4% (n=9), respectively.

Statistical analysis—Data are presented as means and one standard deviation (1 SD). Confidence intervals were calculated on logarithmically transformed data. Comparisons between groups were by the Mann-Whitney U test. Two sided values of $p < 0.05$ were considered significant.

Results

Mean ages were similar in all study groups, and the groups of pregnant women did not differ in weight gain or gestational age.

The mean plasma immunoreactive atrial natriuretic peptide concentration in the normal, non-pregnant subjects was 37.0 (19.1) ng/l (range 7.5-85.0 ng/l) and in the normal pregnant women 56 (29) ng/l (range 21-138 ng/l) (ratio of geometric means 1.5; 95% confidence interval for ratio of means 1.1 to 2.1; $p < 0.02$). A substantial overlap into the normal range was seen (figure). The mean concentration in nine patients with mild pre-eclampsia was 127 (60) ng/l (range 62-256 ng/l), which was significantly higher than in normal pregnancy (ratio of geometric means 2.3; 95% confidence interval for ratio of means 1.4 to 3.9; $p < 0.01$). Compared with the group with mild pre-eclampsia, however, the six patients with severe disease had still higher values (392 (225) ng/l) (range 101-670 ng/l); ratio of geometric means 2.3; 95% confidence interval for ratio of means 1.5 to 5.9; $p < 0.02$). All values were above the normal range (figure).

Discussion

Factors that regulate atrial natriuretic peptide secretion have not been fully determined. It has been reported that plasma immunoreactive atrial natriuretic peptide concentration is positively asso-

Plasma immunoreactive atrial natriuretic peptide concentrations in normal, pregnant, and pre-eclamptic women. Horizontal bars represent group means.

ciated with atrial pressures⁸ and right ventricular end diastolic pressure⁹ and that atrial natriuretic peptide is released into the bloodstream in man in response to atrial stretch caused by expansion of the blood volume.^{10,11} These studies suggest that blood volume and hence atrial pressure govern the release of atrial natriuretic peptide.

As atrial natriuretic peptide is concerned in the control of plasma volume and vascular tone we might expect that plasma immunoreactive atrial natriuretic peptide concentrations in pregnant women would differ from those in non-pregnant controls. Our study confirms that concentrations during pregnancy are increased, as they are in animal models.¹² This may be explained, at least partly, by an increase in blood volume and a concomitant atrial distension. In pre-eclampsia intravascular volume depletion is a prominent feature. This depletion is roughly proportional to the severity of the disease.¹³ In contrast with what might be expected, we found raised concentrations of plasma immunoreactive atrial natriuretic peptide in these patients, with the highest values in those with severe pre-eclampsia. We can only speculate whether these high plasma immunoreactive atrial natriuretic peptide concentrations are due to reduced metabolic clearance or to increased secretion.

The increased plasma immunoreactive atrial natriuretic peptide concentration in pre-eclamptic subjects may reflect a reduced renal clearance owing to a diminished glomerular filtration rate. This is unlikely, however, as the glomerular filtration rate is only rarely below non-pregnant values. A reduction in metabolic clearance in other tissues remains a possibility.

Another reason for the raised concentrations of plasma immunoreactive atrial natriuretic peptide in pre-eclampsia may be the high blood pressure, as circulating concentrations of the peptide are raised in essential hypertension.¹⁴ Though most patients with essential hypertension have normal or low blood volume, central venous pressure and pulmonary capillary wedge pressure are usually high. This may explain the increased production of atrial natriuretic peptide in this condition. In contrast, most pre-eclamptic patients present with low central venous pressure and low pulmonary capillary wedge pressure.¹⁵⁻¹⁷ Hence it seems surprising that pre-eclampsia is associated with increased plasma immunoreactive atrial natriuretic peptide concentrations.

Our findings show that patients with pre-eclampsia have raised

concentrations of plasma immunoreactive atrial natriuretic peptide and that concentrations rise further with the severity of the disease. Notwithstanding reports that atrial natriuretic peptide is released into the plasma in response to increased atrial pressure our results imply that this is not the principal stimulus for the raised concentrations of the peptide in pre-eclampsia.

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Influence of non-steroidal anti-inflammatory drugs on the outcome of faecal occult blood tests in screening for colorectal cancer

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Abstract

Non-steroidal anti-inflammatory drugs have been accused of causing false positive results in faecal occult blood tests for colorectal cancer. A study was therefore performed in 10931 people undergoing faecal occult blood screening tests to assess the effect of these drugs on the predictive value of a positive test result. Those with a positive result were interviewed and a full drug history was taken before they underwent a full colorectal examination. Of the 455 people with a positive result, 50 were taking non-steroidal anti-inflammatory drugs: 10 (20%) had colonic neoplasia. Of the 405 who were not taking non-steroidal anti-inflammatory drugs, 129 (32%) had colonic neoplasia. These detection rates were not significantly different, and the predictive value of a positive result for an adenoma larger than 1 cm was 14% in the group not taking anti-inflammatory drugs and 26% in the group taking them (not significant).

These results suggest that a finding of occult faecal blood cannot be attributed to upper gastrointestinal tract bleeding caused by non-steroidal anti-inflammatory drugs and should be followed by a thorough colorectal examination.

Introduction

There is much evidence linking the ingestion of non-steroidal anti-inflammatory drugs with chronic gastrointestinal bleeding.¹ These

drugs inhibit the synthesis of prostaglandins, which have cytoprotective effects on the upper gastrointestinal tract, as well as suppressing gastric acid secretion.² Testing stool for occult blood is becoming an important means of screening for colorectal neoplasia in individuals over the age of 50,³ for whom non-steroidal anti-inflammatory drugs are widely prescribed. A small study conducted on patients attending a rheumatology clinic suggested that treatment with non-steroidal anti-inflammatory drugs does not lead to false positive faecal occult blood test results,⁴ but another study showed an increase in false positive results in such patients compared with those taking a placebo.⁵ The aim of this study was to establish the effect of ingestion of non-steroidal anti-inflammatory drugs on the predictive value of a positive faecal occult blood test result in population screening for colorectal neoplasia.

Patients, methods, and results

A total of 10931 asymptomatic individuals (aged 50-74 years) underwent faecal occult blood tests in a screening study for colorectal neoplasia. Either a standard guaiac, pseudoperoxidase based test (Hemoccult) or an immunological test (Feca EIA) was completed over a three or six day period. Individuals with positive faecal occult blood test results were interviewed and a full drug history was taken to establish drug ingestion at the time of the test. They then underwent full colonic assessment either by flexible sigmoidoscopy and double contrast barium enema or colonoscopy.

Of the 10931 individuals who completed the faecal occult blood test, 455 had positive results and underwent full colonic investigation. Fifty of these were taking non-steroidal anti-inflammatory drugs at the time of the test, 10 of whom (20%) were found to have colonic neoplasia (three carcinomas, seven adenomas more than 1 cm in size). Of the 405 patients not taking non-steroidal anti-inflammatory drugs at the time of the test, 129 (32%) had neoplastic disease (23 carcinomas, 106 adenomas more than 1 cm in size) (table). These detection rates were not significantly different ($\chi^2=2.9$, $p>0.05$). The predictive value of a positive test result for a colorectal adenoma more than 1 cm in size was 14% (7/50) in the group not taking non-steroidal anti-inflammatory drugs and 26% (106/405) in the group taking them ($\chi^2=3.5$, $p>0.05$).

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