and no further episodes of ventricular fibrillation occurred. Arterial blood gas tensions at this time were pH 7·3, oxygen pressure 50·7 kPa (380 mm Hg), and carbon dioxide pressure 6·4 kPa (48 mm Hg); standard bicarbonate concentration 21·5 mmol(mEq)/l; and base excess −2·5 mmol(mEq)/l.

Amiodarone was continued as an intravenous infusion with 600 mg in 5% dextrose over 12 hours and 300 mg in 5% dextrose for a further 24 hours, during which time an electrocardiogram showed varying degrees of heart block and nodal rhythms. His clinical state improved, and he required only intravenous atropine on two occasions for bradycardia. Serum digoxin concentration was above 5 μg/l on admission, but the sample was not retained for more accurate determination. Digoxin concentrations did not fall into the therapeutic range until day 5, when a concentration of 1·4 μg/l was recorded. As the plasma half life in overdosage is about 13 hours[3] the peak digoxin concentration would have been over 40 μg/l.

Comment

Serum digoxin concentrations were not obtained accurately in this patient, although he was undoubtedly severely poisoned and had intractable ventricular fibrillation unresponsive to a class I anti-arrhythmic drug. Use of a beta blocker was thought too hazardous because of the absence of pacing facilities and the previous asystole. Amiodarone is a class III antiarrhythmic drug that prolongs the action potential in ventricular muscle, lengthens the refractory period of the myocardium, and reduces the maximum rate of repolarisation. Drugs exhibiting class III antiarrhythmic properties reverse arrhythmias induced with ouabain in animals.[4]

Although amiodarone increases digoxin concentrations when given by mouth and this may produce digoxin toxicity after chronic administration,[5] this phenomenon should not exclude use of amiodarone in digoxin overdosage, as shown by this case. Further work should be undertaken to confirm the usefulness of amiodarone in digoxin overdosage. We believe that its ability to reduce excitability at all levels probably contributed to the survival of this patient, who was discharged fit and well eight days after admission.

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Middlesbrough General Hospital, Cleveland TS5 5AZ

R MAHESWARAN, MB, CHB, senior house officer
M G BRAMBLE, MD, MRCP, consultant physician
C A HARDISTY, MD, MRCP, consultant physician

Correspondence to: Dr M G Bramble.

Failure of increased use of endoscopy to influence complication rate in peptic ulcer disease

In an attempt to rationalise the increasing use of upper gastrointestinal endoscopy, we and others have described a direct referral open access endoscopy service for general practitioners.[1-3] Although the service is popular with general practitioners and may reduce referrals to hospital, it does result in a considerable increase in the number of endoscopies being performed,[2] which is time consuming and expensive. To justify this it is therefore important to document carefully any effects of this increased use of endoscopy on the course of gastrointestinal disease. By comparing three different areas with varying endoscopic practices we have shown that open access endoscopy is unlikely to influence the prognosis of gastric cancer, as the proportion of early lesions found is not increased.[4] We now report its effect on hospital admissions for the major complications of peptic ulcer disease.

Patients, methods, and results

We compared the hospital admission rates for two specific, easily identifiable complications of peptic ulcer disease in three district general hospitals in Wessex with differing endoscopic practice (table). In centre A there was an open access general practitioner endoscopy service, in centre B a freely available hospital based service, and in centre C a limited hospital service only. The yearly numbers of endoscopies performed in these centres were roughly 1130, 540, and 150 per 100 000 population served. The mean admission rates a year for the major complications of peptic ulcer disease (perforation or haemorrhage) were obtained from the Hospital Activity Analysis for the five years before the increased use of endoscopy (1968-72) and for five years after it had been established (1976-80).

Admission rates for complications of peptic ulcer disease per 100 000 population served by each centre. Values shown are for haemorrhage (values for perforation given in parentheses)

Centre	Endoscopic practice	Approximate No of endoscopies performed/ 100 000 population	Duodenal ulcer		Gastric ulcer	
			1968-72	1976-80	1968-72	1976-80
A	General practitioner plus outpatient	1130	17·9 (9·1)	22·5 (11·2)	9·9 (2·1)	9·9 (2·1)
B	Outpatient	580	8·0 (7·0)	7·7 (7·5)	5·1 (1·5)	5·5 (1·5)
C	Limited outpatient	150	5·0 (6·8)	5·6 (7·1)	3·8 (2·2)	4·6 (1·4)

Although the frequency of haematemesis and perforation varied between centres, presumably secondary to the characteristics of the populations served, within each centre the complication rate remained remarkably constant, and there was no evidence that the increased use of endoscopy had any effect on the complication rate of peptic ulcer disease (table). Retrospective review of 100 patients admitted with these complications showed that although 65 of them had a history of diagnosed peptic ulcer disease, only 35 had symptoms at the time of admission and only eight had been given specific antiulcer treatment before admission. Indeed, fewer than 10 had visited their general practitioner in the four weeks before hospital admission with the major complication.

Comment

Although in many instances the Hospital Activity Analysis may not be accurate, as it depends on correct documentation at the time of hospital admission, the analysis for such major complications as haemorrhage and particularly perforation should be reasonably correct because of their ready confirmation and the accuracy of diagnosis.[5] Within these limitations the evidence presented does not suggest that the increased use of endoscopy which results from the introduction of an open access endoscopy service is likely to influence the incidence of such major complications of peptic ulcer disease. One explanation of this emerged from the study of patients admitted with these complications, as it became clear that few of these patients had attended their general practitioners in the weeks before admission and thus were not likely to benefit from more freely available endoscopic services.

The years covered by this report also saw the introduction of H_2 antagonists, and the results might suggest that these also had no major effect on the complication rate, probably for the same reasons discussed above.

This study, together with our previous ones, suggests that the provision of an open access endoscopy service in its present form has little to offer in terms of altering disease course. The best approach towards reducing the complication rate in peptic ulcer disease is probably one directed at encouraging those patients at risk—for example, those with known peptic ulcer disease—to seek help earlier if their symptoms recur.

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Southampton General Hospital, Southampton SO9 4XY
G HOLDSTOCK, DM, MRCP, senior registrar in medicine
S COLLEY, MB, BS, registrar in medicine

Correspondence to: Dr G Holdstock, Professorial Medical Unit, Level D, South Laboratory and Pathology Block, Southampton General Hospital, Southampton SO9 4XY.

Serum free thyroxine and free triiodothyronine concentrations in pregnancy

Measurements of circulating free thyroid hormone concentrations are generally considered to be an accurate index of thyroid state. It has been reported, however, that the serum concentration of free thyroxine falls during pregnancy,[1] which is at variance with the euthyroid clinical state of pregnant women. A new method for direct radioimmunoassay of serum free triiodothyronine concentrations has been developed.[2] In this study we measured serum free triiodothyronine as well as free thyroxine concentrations throughout pregnancy and compared the values obtained with predicted values derived from total hormone and binding protein concentrations.

Patients, methods, and results

Blood was taken from women in each trimester of pregnancy at routine antenatal visits. Further samples were collected from an age matched control group of euthyroid women taking no medication.

Free triiodothyronine and free thyroxine concentrations were measured by direct radioimmunoassay (Amerlex Kit methods, Amersham International, Amersham, Buckinghamshire).[2] These free hormone assays use thyroxine and triiodothyronine derivatives labelled with iodine-125 that have been chemically modified to inhibit severely their binding to serum thyroid hormone binding proteins but that bind normally to thyroxine or triiodothyronine antibodies. In the assays free thyroid hormones and the modified labelled derivatives compete for binding to high affinity thyroxine or triiodothyronine antibodies, and the proportion of labelled derivative bound to the antibody is inversely related to the serum free thyroxine or free triiodothyronine concentration. Total serum triiodothyronine and thyroxine concentrations were measured by in house radioimmunoassay, thyroxine binding globulin concentration by immunoelectrophoresis, and thyroxine binding prealbumin and albumin concentrations by immunodiffusion. Predicted free triiodothyronine and free thyroxine concentrations were derived from total hormone and binding protein concentrations, using a method taking into account the known binding characteristics of the thyroid hormone binding proteins.[3]

Serum thyroxine binding globulin and total thyroxine concentrations rose during pregnancy, whereas concentrations of free thyroxine and free triiodothyronine were progressively lower in each trimester (table). The changes in measured free thyroxine and free triiodothyronine were paralleled by a reduction in predicted free hormone concentrations.

Mean (SD) concentrations of free thyroxine and triiodothyronine in pregnant women and euthyroid controls

Subjects	Thyroxine binding globulin (mg/l)	Total thyroxine (nmol/l)	Free thyroxine (pmol/l)		Free triiodothyronine (pmol/l)	
			Predicted	Measured	Predicted	Measured
Controls (n = 20)	9·9 (1·9)	80·5 (19·0)	22·1 (6·6)	17·0 (2·7)	5·8 (1·3)	6·6 (1·1)
Pregnant women:						
1st trimester (n = 16)	17·2* (2·6)	113·0* (18·1)	19·8 (4·0)	13·8† (2·0)	4·2† (0·8)	5·4 (0·8)
2nd trimester (n = 18)	24·3* (3·8)	119·0* (29·6)	14·2* (3·1)	11·3* (1·7)	2·9* (0·7)	4·4* (1·2)
3rd trimester (n = 19)	27·4* (3·4)	126·0* (29·3)	14·1* (4·7)	10·9* (1·8)	3·2* (1·0)	4·2* (0·7)

Significance of difference from control group (Student's *t* test for unpaired data): *p < 0·0005; †p < 0·0025.
Conversion: SI to traditional units—Thyroxine: 1 nmol/l ≈ 77·7 ng/100 ml. Free thyroxine: 1 pmol/l ≈ 77·7 pg/100 ml. Free triiodothyronine: 1 pmol/l ≈ 65 pg/100 ml.

Comment

Both measured and predicted free triiodothyronine and free thyroxine concentrations were low in the pregnant women. These changes were most pronounced in the third trimester but were already evident in the first, as were changes in thyroxine binding globulin and total thyroxine concentrations. The low free hormone concentrations were not, however, an artefact of the technique in the presence of high concentrations of thyroxine binding globulin since free triiodothyronine and free thyroxine concentrations are normal in subjects in whom concentrations of thyroxine binding globulin are even higher than during pregnancy.[4]

The pregnant women showed none of the clinical features of hypothyroidism despite low circulating free hormone concentrations. The maintenance of a clinically euthyroid state in the face of low free hormone concentrations suggests that pregnancy induced a change in the cellular response to thyroid hormones. We propose that in pregnancy there may be an oestrogen induced alteration in cellular uptake or nuclear receptor binding of thyroid hormones that is countered by a fall in circulating free hormone concentrations. With the increasing use of measurements of free thyroid hormone concentrations as routine thyroid function tests it should be remembered that a lower reference range is appropriate in pregnancy.

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Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Birmingham B15 2TH
JAYNE A FRANKLYN, MB, MRCP, research fellow
M C SHEPPARD, PHD, MRCP, Wellcome Trust senior lecturer
D B RAMSDEN, PHD, FRSC, senior lecturer

Correspondence to: Dr J A Franklyn.