Changes in pain score and respiratory function after intrathecal injection of 4 mg morphine. Naloxone was given after the 12-hour observations.

	Hours after injection					
	0	4	12	16	24	44
Pain score*	8	0	0	0	0	8
Pao ₂ (kPa)			6.8	10.2	7.7	10.3
F _i O ₂			0.21	0.28	0.21	0.21
Paco ₂ (kPa)			7.25	6.62	6.25	4.63
Respiratory rate (breaths/min)	16	12	8	20	12	14
Heart rate (beats/min)	90	80	120	110	75	100

*0 = No pain; 10 = worst pain imaginable.

Pao₂ = Arterial oxygen pressure. F_iO₂ = Fractional inspired oxygen. Paco₂ = Arterial carbon dioxide pressure.

Conversion: SI to traditional units—Pao₂ and Paco₂: 1 kPa ≈ 7.5 mm Hg.

Twelve hours after injection he was conscious but confused, responding to pin prick and tibial compression. He was cyanosed, his skin cold and sweaty, pulse 120/min, blood pressure 130/80 mm Hg, and respiratory rate 8/min (table). He was eructating and retching every five minutes. He was given naloxone 0.4 mg intravenously and 0.4 mg intramuscularly: his respiratory rate became 20/min and pulse 80/min. His conscious state improved rapidly but he could not recall events post spinal injection. He was given naloxone 0.4 mg intravenously 45 minutes later and a naloxone intravenous infusion of 0.2 mg/h for four hours. He remained lucid and in a satisfactory cardiovascular and respiratory state, though his degree of analgesia remained unaltered.

Comment

This case shows an important respiratory side effect of subarachnoid morphine and presents the paradox that under these circumstances naloxone did not reverse the pain relief yet reversed the respiratory depression. The use of hypobaric morphine sulphate solution (SG 1-005) and a large dose (4 mg) compared with that used by Wang *et al*³ (0.5–1.0 mg) may have been responsible for the respiratory depression. Based on the interval between intrathecal injection and onset of respiratory depression the time taken for morphine to diffuse up the spinal fluid to the medulla was about eight hours. Reversal of respiratory and other medullary effects without abolition of pain relief with naloxone leads us to suggest three hypotheses.

Firstly, the morphine concentration and therefore the percentage of receptors occupied by morphine will be highest nearest the site of application. While naloxone competes well with morphine for receptor occupancy in the medulla, where the morphine concentration may be similar to that achieved when the drug is given intravenously, the morphine concentration in the substantia gelatinosa will be far above that for effective competition by naloxone for reversal of pain relief. Secondly, two pharmacologically distinct morphine receptors may exist—associated with analgesia or respiratory depression—and different kinetics may obtain for naloxone-morphine interaction at these two groups of receptors. Finally, naloxone may have reversed all the effects of morphine. Since the reverberating cycle for pain had been interrupted, however, the pain may have been relieved for a considerable time.

Although few reports exist of intrathecal morphine being used to relieve chronic pain, this is an excellent method of achieving prolonged analgesia if administered in a hyperbaric solution⁴ such as 10% dextrose, so that various levels of analgesia may be selected.

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Division of Anaesthesia, Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex HA1 3UJ

R D M JONES, FFRACs, senior registrar

J G JONES, MD, MRCP, FFRACs, consultant member of scientific staff, Medical Research Council

Effects on human thyroid function of sulphonamide and trimethoprim combination drugs

Sulphonamides in fixed combination with trimethoprim are widely prescribed by clinicians as antibacterial agents; in 1978, 5½ million prescriptions for co-trimoxazole were given in Great Britain.¹ Sulphur-containing drugs such as sulphonylureas are known to lower thyroid hormone concentrations and are routinely used in treating thyrotoxicosis. We have therefore examined the effects on thyroid function in man of co-trimoxazole (trimethoprim 80 mg and sulphamethoxazole 400 mg/tablet) and co-trifamole (trimethoprim 80 mg and sulphamoxole 400 mg/tablet) and have observed a fall in circulating thyroid hormone concentrations.

Patients, methods, and results

We used identical protocols in our two separate double-blind crossover studies; the first was in men, the second in women. In each study 10 men or women were randomly allocated to one of two groups: in the first part of the study half the volunteers received co-trimoxazole (in the recommended dose of two tablets twice daily); during the second part these volunteers received co-trifamole in the recommended dose (two tablets immediately, thereafter one tablet twice daily). The remaining volunteers received these treatments in reverse order. Each treatment period was for 10 days and there was a three-week washout period between treatments. The volunteers had no clinical or laboratory evidence of thyroid, renal, or hepatic dysfunction and none was taking drugs.

Effect of sulphonamide and trimethoprim combination drugs on thyroid hormone concentrations. Results are means $\pm$ 1SD

	T4 (nmol/l)	Free thyroxine index	T3 (nmol/l)	Thyroid-stimulating hormone (mU/l)
<i>Study 1: men</i>				
Co-trimoxazole:				
Before ..	97.10 $\pm$ 15.58	95.20 $\pm$ 18.15	2.33 $\pm$ 0.37	2.81 $\pm$ 0.79
After ..	83.00 $\pm$ 14.97	82.61 $\pm$ 12.52	1.96 $\pm$ 0.24	2.42 $\pm$ 1.18
p Value ..	<0.002	<0.002	<0.006	NS
Co-trifamole:				
Before ..	97.20 $\pm$ 18.05	96.33 $\pm$ 16.14	2.50 $\pm$ 0.42	2.66 $\pm$ 1.25
After ..	96.90 $\pm$ 14.33	92.14 $\pm$ 13.82	2.17 $\pm$ 0.23	2.86 $\pm$ 1.25
p Value ..	NS	NS	<0.05	NS
<i>Study 2: women</i>				
Co-trimoxazole:				
Before ..	92.60 $\pm$ 8.91	90.10 $\pm$ 7.36	1.76 $\pm$ 0.27	3.38 $\pm$ 0.85
After ..	87.20 $\pm$ 9.03	86.35 $\pm$ 7.40	1.53 $\pm$ 0.28	3.04 $\pm$ 0.91
p Value ..	<0.03	<0.02	<0.04	NS
Co-trifamole:				
Before ..	99.20 $\pm$ 13.38	99.24 $\pm$ 13.38	1.90 $\pm$ 0.33	3.19 $\pm$ 0.89
After ..	90.60 $\pm$ 12.29	89.94 $\pm$ 13.26	1.65 $\pm$ 0.32	3.11 $\pm$ 0.89
p Value ..	NS	NS	<0.03	NS

NS = Not significant.

Conversion: SI to traditional units—T4: 1 nmol/l = 0.08 μ g/100 ml. T3: 1 nmol/l = 0.65 ng/ml.

Serum was assayed for total thyroxine (T4), tri-iodothyronine (T3), and thyroid-stimulating hormone concentrations, and the free thyroxine index was calculated at the beginning and end of each 10-day treatment period. Two spot-checks of serum sulphonamide were made during treatment to confirm compliance with instructions. Serum T4 and T3 were determined by the methods of Challand *et al*.² The free thyroxine index was derived from the total T4 value and the result of the T3 resin uptake test³ (Thyopac 3; Radiochemical Centre). Serum thyroid-stimulating hormone concentrations were measured by using a double antibody radioimmunoassay procedure based on that of Hall *et al*.⁴ All specimens from one individual were analysed in a single batch. We used the paired *t* test for statistical analysis. Spiked samples showed that the T4 and T3 results obtained from pooled normal serum were not affected by sulphamoxole (200 mg/l), sulphamethoxazole (220 mg/l), or trimethoprim (100 mg/l).

Our table shows that co-trimoxazole significantly lowered T3, T4, and the free thyroxine index in both sexes while co-trifamole significantly lowered T3 concentrations only. Thyroid-stimulating hormone values did not alter significantly. All subjects had satisfactory sulphonamide concentrations (14–140 μ g/l).

Comment

Our study is the first to show that sulphonamide and trimethoprim combination drugs lower thyroid hormone concentrations; the greater effect of co-trimoxazole probably reflects the larger quantity of sulphonamide ingested. In no subject did the peripheral thyroid

hormone concentrations fall below the reference range for our laboratory (T4: 55-144 nmol/l (4.3-11.2 µg/100 ml), T3: 0.9-2.8 nmol/l (0.6-1.8 ng/ml)), and thyroid-stimulating hormone concentrations did not rise. Thus it cannot be concluded from this study of 10-day periods of drug treatment that these drugs cause hypothyroidism; nevertheless, this remains a possibility when the drugs are given for longer periods. The mechanism by which these drugs lower thyroid hormone concentrations is unknown but they may, like the sulphonylureas, reduce conversion of iodine to the organic form, possibly by inhibiting peroxidase.⁵

Although this fall in peripheral thyroid hormone values in these normal subjects on combined trimethoprim-sulphonamide treatment was small we think that it is a cause for concern. In the light of these findings we recommend that tests of thyroid function should be interpreted with caution in patients on such treatment, and subjects who have been prescribed these agents for long-term use should have their thyroid function regularly assessed.

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University Departments of Medicine and Clinical Biochemistry, Royal Infirmary, Glasgow G4 0SF

HOWARD N COHEN, MB, MRCP, senior registrar in medicine

G H BEASTALL, PhD, principal biochemist

W A RATCLIFFE, PhD, senior biochemist

C GRAY, PhD, senior biochemist

I D WATSON, MSC, FIMLS, senior biochemist

J A THOMSON, MD, FRCP, consultant physician

Severe hypophosphataemic osteomalacia with primary hyperparathyroidism

Osteomalacia is rare in primary hyperparathyroidism. Characteristically, the serum calcium concentration is normal in primary hyperparathyroidism complicated by vitamin-D-deficient osteomalacia but hypercalcaemia develops quickly after administration of vitamin D.^{1,2} We have studied a patient with hypercalcaemic primary hyperparathyroidism who presented with hypophosphataemic osteomalacia. Vitamin D treatment produced a rise in serum inorganic phosphate concentration associated with bone healing but no consistent change in serum calcium concentration.

Case report

The patient, a 48-year-old married woman with no previous illness, presented in 1973 with an eight-month history of diffuse and severe bone pains, weakness and muscle wasting, and difficulty in walking. She was unable to stand erect from the sitting position. Pressure applied to her ribcage produced spontaneous severe pain. Skeletal x-ray films showed multiple rib fractures but no obvious subperiosteal erosion. Bone histology showed severe osteomalacia with osteoid 29% total trabecular bone volume (equivalent to 85% bone matrix). Plasma concentrations were: calcium 3.2 mmol/l (12.8 mg/100 ml), inorganic phosphate 0.5 mmol/l (1.5 mg/100 ml), creatinine 60 µmol/l (0.7 mg/100 ml), magnesium 0.76 mmol/l (1.8 mg/100 µl), alkaline phosphatase 20 KA units, parathyroid hormone 1.9 ng/ml (normal up to 1.0 ng/ml), and 25-hydroxy vitamin D 33 nmol/l (13 ng/ml) (normal 13-88 nmol/l; 5-35 ng/ml). A 24-hour collection of urine contained hydroxyproline 596 µmol/l (7.8 mg/100 ml), calcium 3.02 mmol/l (12 mg/100 ml), and inorganic phosphate 11.5 mmol/l (36 mg/100 ml). Dietary vitamin D intake was normal. A jejunal biopsy specimen and barium studies of the small bowel were normal. Hyperparathyroidism with osteomalacia was diagnosed. She refused neck exploration.

Oral ergocalciferol was started at 50 000 IU/day and gradually increased to 200 000 IU/day. Bone pain persisted for several months but gradually decreased, while walking capacity and muscle power improved. Clinical

recovery was complete after 12 months and the treatment stopped. She was seen intermittently during 1975 and then lost to follow-up until October 1977. She then complained of muscle weakness and difficulty in walking but no bone pain. She was persuaded to undergo parathyroid surgery, and an adenoma was removed (Mr J S Waters). Muscle strength returned quickly postoperatively, and she remained well.

The figure shows the changes in plasma concentrations and bone osteoid content. At presentation plasma concentration of parathyroid hormone and

Effect of treatment with vitamin D₂. A rise in serum inorganic concentration was followed by a fall in serum alkaline phosphatase activity and considerable, but not complete, bone healing as shown by serial estimation of osteoid. Serum calcium and inorganic phosphate concentrations were eventually corrected by parathyroidectomy. Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml. Phosphate: 1 mmol/l ≈ 3 mg/100 ml. 25-Hydroxy vitamin D: 1 nmol/l ≈ 0.4 ng/ml.

calcium were raised while those of phosphate were low and of 25-hydroxy vitamin D normal. During vitamin D treatment plasma concentrations of calcium remained raised though those of parathyroid hormone fell to within the normal range. Alkaline phosphatase activity rose and then fell, while plasma phosphate concentrations rose and remained at the lower end of the normal range. Plasma 25-hydroxy vitamin D concentrations rose rapidly to a maximum of 425 nmol/l (170 ng/ml), when calcium absorption measured by a double isotope technique was 95%.³ Sequential bone biopsies showed a progressive reduction in the amount of osteoid, though this was never normalised. Plasma biochemistry became normal after parathyroidectomy and remained so. Postoperative maximum tubular reabsorption capacity for phosphate was 1.07 mmol/l (3.3 mg/100 mg) (normal 0.7-1.4 mmol; 2.2-4.3 mg/100 ml), indicating that renal phosphate handling was then normal.

Comment

This patient is unusual because she presented with severe osteomalacia, the hypercalcaemia being an unexpected observation. She