SHORT REPORTS

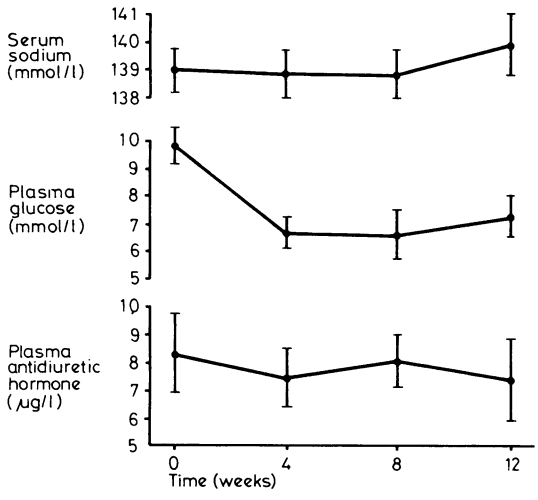
Response of antidiuretic hormone to chlorpropamide

Chlorpropamide has been used to treat diabetes insipidus since 1966,[1] but its mode of action is still not entirely clear. There is good agreement that it augments the renal effects of endogenous antidiuretic hormone,[2] but it might also cause pituitary release.[3] To help clarify this we have measured serial plasma concentrations of antidiuretic hormone in a group of patients receiving long-term chlorpropamide.

Patients, methods, and results

Eleven patients with maturity-onset diabetes (two women; age range 38-66 years, mean 56 years) requiring treatment with oral hypoglycaemics were studied. All were receiving conventional dietary advice. Blood was taken from an antecubital vein (after 30 minutes' sitting and overnight fast) before and four, eight, and 12 weeks after they started taking 250 mg chlorpropamide daily. Plasma concentrations of antidiuretic hormone were measured by radioimmunoassay (normal range 4-12 μg/l). This method is reliable in assaying both normal and raised concentrations.[4] Serum sodium and plasma glucose concentrations were measured by routine automated analysis. No change in chlorpropamide dosage was made during the study. All patients had normal renal function. Changes in measurements were assessed by Student's *t* test.

Serum sodium concentration did not change throughout the study (figure), and no patient developed hyponatraemia. Blood glucose concentration had fallen significantly by four weeks ($p < 0.001$) but was unchanged thereafter. Plasma osmolality stayed within the normal range throughout the study. Plasma concentrations of antidiuretic hormone did not change significantly during the study.



Mean ± SEM changes in serum concentrations of sodium and plasma concentrations of glucose and antidiuretic hormone during treatment with chlorpropamide.
Conversion: SI to traditional units—Sodium: 1 mmol/l = 1 mEq/l. Glucose: 1 mmol/l ≈ 18 mg/100 ml.

Comment

Defects of free water clearance may occur in normal subjects and in patients with diabetes mellitus receiving chlorpropamide even in the absence of hyponatraemia.[2] If this defect is partly due to an increase in secretion of antidiuretic hormone then plasma concentrations of the hormone should rise during chlorpropamide treatment. We were unable to show any such rise over 12 weeks in patients treated with 250 mg chlorpropamide daily. As no patient developed hyponatraemia, however, we cannot state with certainty that secretion of antidiuretic hormone would not increase in that condition. We think that a larger dose of chlorpropamide would be unlikely to increase concentrations of antidiuretic hormone, as 250 mg/day has been used effectively to treat diabetes insipidus and hyponatraemia has been recorded with this dosage.[5]

Peripheral augmentation of the effects of antidiuretic hormone explains why chlorpropamide causes antidiuresis in patients who have the capability of releasing antidiuretic hormone but not in patients or animals who have no residual production of the hormone. We have seen chlorpropamide used effectively in the treatment of diabetes insipidus without any change in plasma concentrations of antidiuretic hormone (unpublishcd observation). We could not show a rise in plasma concentrations of antidiuretic hormone with the chlorpropamide dosage used, and while these data do not preclude an acute effect on release of the hormone,[3] chlorpropamide given long term seems unlikely to act direct on the pituitary or hypothalamus causing such release.

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Intrathecal morphine: naloxone reverses respiratory depression but not analgesia

Since opiate receptors were localised in the brain and substantia gelatinosa of the spinal cord[1] clinicians have been attempting to obtain relief of pain by administering endorphins[2] and morphine[3 4] directly into the spinal subarachnoid space. We report on a patient who developed respiratory depression, vomiting, amnesia, and urinary retention after receiving intrathecal morphine.

Case history

A 63-year-old man was admitted with a six-month history of intermittent claudication. He had diabetes treated by diet, and hyperlipidaemia of one year's duration treated with clofibrate. After femoral arteriography, left lumbar sympathectomy was performed one month before admission. Two weeks before admission he developed severe burning pain in both feet and calves, which responded poorly to treatment with distalgesic (dextropropoxyphene and paracetamol), papaveretum, and carbamazepine. The pain was thought to be causalgic; however, he had no clinical evidence of peripheral neuropathy.

Because of the poor response to 60 mg papaveretum given over 24 hours we evaluated his responses to intrathecal morphine. A 25-gauge spinal needle was introduced at the Ll-2 interspace and 4 mg morphine sulphate in 0·4 ml water (morphine sulphate stabilised with sodium metabisulphite 0·1% w/w 10 g/l; Evans Medical) mixed with 0·5 ml cerebrospinal fluid and introduced intrathecally. Complete relief of pain occurred within 15 minutes of injection; pulse and respiratory rates and blood pressure were normal, and he was sleepy but rousable. Pain relief was assessed by a visual analogue scale[5] (table). Complete relief lasted for 40 hours, compared with 10-24 hours in another study.[3]

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
Pa_{O_2} (kPa)			6·8	10·2	7·7	10·3
$F_{I}O_2$			0·21	0·28	0·21	0·21
Pa_{CO_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.
Pa_{O_2} = Arterial oxygen pressure. $F_{I}O_2$ = Fractional inspired oxygen. Pa_{CO_2} = Arterial carbon dioxide pressure.
Conversion: SI to traditional units—Pa_{O_2} and Pa_{CO_2}: 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 solution[4] such as 10% dextrose, so that various levels of analgesia may be selected.

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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 ±1SD

	T4 (nmol/l)	Free thyroxine index	T3 (nmol/l)	Thyroid-stimulating hormone (mU/l)
	Study 1: men			
Co-trimoxazole:				
Before	97·10±15·58	95·20±18·15	2·33±0·37	2·81±0·79
After	83·00±14·97	82·61±12·52	1·96±0·24	2·42±1·18
p Value ..	<0·002	<0·002	<0·006	NS
Co-trifamole:				
Before	97·20±18·05	96·33±16·14	2·50±0·42	2·66±1·25
After	96·90±14·33	92·14±13·82	2·17±0·23	2·86±1·25
p Value	NS	NS	<0·05	NS
	Study 2: women			
Co-trimoxazole:				
Before	92·60±8·91	90·10±7·36	1·76±0·27	3·38±0·85
After	87·20±9·03	86·35±7·40	1·53±0·28	3·04±0·91
p Value ..	<0·03	<0·02	<0·04	NS
Co-trifamole:				
Before	99·20±13·38	99·24±13·38	1·90±0·33	3·19±0·89
After	90·60±12·29	89·94±13·26	1·65±0·32	3·11±0·89
p Value ..	NS	NS	<0·03	NS

NS = Not significant.
Conversion: SI to traditional units—T4: 1 nmol/l = 0·08 μg/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 test[3] (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 μg/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