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Stoke Mandeville Hospital, Aylesbury, Bucks HP21 8AL
M D L MORGAN, MB, MRCP, registrar
B V SINGH, MB, BS, senior house officer
M H FRAME, PHD, clinical scientist, Astra clinical research unit
S J WILLIAMS, MB, MRCP, consultant physician

Antihypertensive treatment with beta-blockers in patients aged over 65

The use of beta-blockers in elderly patients with hypertension has been questioned owing to the increased incidence of heart failure in this age group. As our clinical impression at the outpatient hypertension clinic was that beta-blockers were well tolerated by elderly patients,[1] we decided to analyse the use and tolerability of beta-blockers in all patients over 65 who were being treated with these drugs, with special reference to the occurrence of heart failure.

Patients, methods, and results

A total of 301 patients aged over 65 years were being treated at the clinic. Two hundred and seventeen of these were aged from 65 to 69, 58 from 70 to 74, and 26 over 75.

Each year the doctors complete a computer record form for each patient with standardised questions about the case history, current antihypertensive treatment, side effects, and reasons for changes in treatment. Dyspnoea on exertion was diagnosed as heart failure if treatment with diuretics or digitalis was indicated.

Analysis of the prescription of beta-blockers in the different groups showed that three-quarters of the patients from 65 to 74 years and half of those aged over 75 were receiving beta-blockade. Analysis of the total treatment showed that 42 (14%) were receiving beta-blockers alone, 51 (17%) were receiving diuretics alone, and 193 (64%) were receiving combined treatment with beta-blockers and diuretics or other drug combinations; 15 (5%) were receiving no treatment. The mean dose for the two most commonly used beta-blockers was 189 mg/day for the $beta_1$-selective metoprolol and 252 mg/day for the non-selective propranolol.

Analysis of the blood pressures showed good pressure control of 156/91 mm Hg in those aged 65-69, 166/94 mm Hg in those aged 70-74, and 174/93 mm Hg in those aged over 75.

Changes of the beta-blocker medication fell into three groups: discontinuation (21 patients (10%)), reduction of the dose (12 patients (5·5%)), and change to another type (49 patients (22·5%))—for example, from a non-selective to a $beta_1$-selective blocker (30 patients (14%)). The reasons for changing from a non-selective to a $beta_1$-selective blocker were similar to those leading to withdrawal of beta-blockade (see table).

Heart failure was diagnosed in 23 patients, of whom 16 (70%) were on beta-blockade in combination with diuretics, digitalis, or both.

Reason for withdrawal of beta-blockers

	No	%
Sleep disturbances	1	0·5
Gastrointestinal symptoms	2	1·0
Obstructive lung disease and/or dyspnoea	3	1·4
Tiredness	2	1·0
Exanthema	2	1·0
Cold hands or feet	1	0·5
Bradycardia	3	1·4
Heart failure (without digitalis)*	1	0·5
Heart failure (on digitalis)	1	0·5
Diabetes mellitus	1	0·5
Reason not stated	4	1·8
Total	21	9·7

* Treatment with a $beta_1$-selective blocker was resumed after giving the patient digitalis.

Comments

This analysis showed that the beta-blockers were generally well tolerated in hypertensive patients over 65. The side effects and patterns of dosage resembled those seen in younger age groups. Heart failure was the reason for discontinuing the treatment in only one patient. Most of the side effects could be overcome by changing from a non-selective to a $beta_1$-selective blocker or by reducing the dose.

Heart failure was diagnosed in 23 patients (11%) and of these patients 16 (70%) were receiving beta-blockade in combination with diuretics or digitalis. In many of these patients symptoms of heart failure might have been due not to bad systolic contraction but to poor filling in stiff hearts. Even at heart rates as low as 120 beats/min the filling time becomes critical to the elderly heart.[2] If the heart rate falls from 100 to 70 beats/min the diastolic filling time increases by 100% without the ejection time being affected.[3] This favourable effect of beta-blockers on the diastolic filling is probably particularly important in the aged, stiff, hypertensive heart.

Beta-blockers have been claimed to reduce the incidence of coronary heart disease.[4] If good efficacy and tolerance is achieved with beta-blockers alone or in combination with other drugs in elderly patients with hypertension this could be important since the incidence of coronary heart disease is increasing with age in both men and women and since coronary heart disease is the most common end-point in hypertension.[5]

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Outpatient Hypertension Clinic, Department of Medicine I, Sahlgrenska Hospital, University of Göteburg, Sweden
JOHN WIKSTRAND, MD, associate professor of clinical physiology
GÖRAN BERGLUND, MD, associate professor of medicine

High plasma calcitonin concentrations in chronic bronchitis

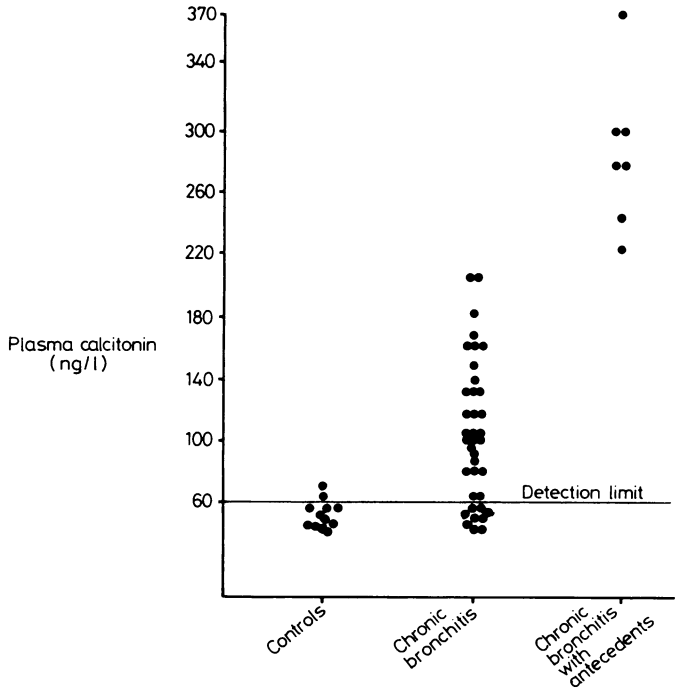
Studies of extrathyroidal and extraultimobranchial production of calcitonin showed calcitonin-like immunoreactivity in brain and lung of lizards and pigeons.[1] Immunofluorescence studies and electron microscopy of lizard lung showed secretory granules of calcitonin-like material in what were apparently Kulchitsky cells.[2] Other workers had found Kulchitsky cells in human bronchial and bronchiolar epithelium and had also isolated calcitonin-like material from human lung.[3]

In chronic bronchitis the acini of mucous glands contain increased numbers of mucus-secreting cells. If Kulchitsky cells were similarly increased patients with chronic bronchitis might be expected to have raised circulating calcitonin concentrations. To test this hypothesis we measured plasma calcitonin concentrations in patients with mucopurulent disease and in a group of healthy, non-smoking controls. We also looked to see if there was some correlation between the plasma calcitonin concentrations and the cumulative numbers of cigarettes smoked during life.

Subjects, methods, and results

The study group comprised 45 men aged 36-78 years (mean 58·9) with chronic mucopurulent bronchitis.[4] All were smokers or ex-smokers of cigarettes. Measurements were made during a quiescent phase of their illness when they were clear of acute infection and had stable blood gas values. None was taking any medication. Twelve healthy men aged 29-76 years (mean 55·0 years) who had never smoked served as controls.

Fasting venous blood was collected at 9 am into cooled heparinised tubes and centrifuged immediately, the plasma being stored at −20°C until assay. Calcitonin was measured in the plasma by direct immunoassay[5] (five days of incubation) with a detection limit of 6·0 pg/tube and an intra-assay variation of under 10%. All samples were assayed at the same time. Statistical evaluation was with the χ^2 test for variables with large numbers of undetectable values and the correlation calculated with Spearman's correlation coefficient.



Plasma calcitonin concentrations in controls, patients with chronic bronchitis, and patients with chronic bronchitis and familiar antecedents of chronic bronchitis or lung cancer.

Of the 45 patients, 34 had plasma calcitonin concentrations above the highest value (80 ng/l) recorded in the controls ($p < 0·001$; fig). There was no correlation between the plasma calcitonin concentrations and total numbers of cigarettes smoked during life ($r = 0·239$; $p > 0·05$), nor was there a significant difference in concentrations between patients who had given up smoking and those who had carried on ($p > 0·05$). A subgroup of seven patients found to have familiar antecedents of chronic bronchitis or lung cancer had the highest plasma calcitonin concentrations recorded in the study (>220 ng/l; fig).

Comment

In mammals and submammalian vertebrates the main sources of calcitonin are the thyroid and ultimobranchial gland, respectively; in lizards, however, calcitonin is isolated from lung.[2] Immunochemical studies have also shown a calcitonin-like material in lizard lung and in bronchial and bronchiolar Kulchitsky cells of man.[2 3]

In our study patients with chronic mucopurulent bronchitis had significantly increased plasma calcitonin concentrations. Whether such high values occur in simple and obstructive chronic bronchitis remains to be determined. That the subgroup of patients with familiar antecedents of chronic bronchitis or lung cancer had the highest concentrations suggests that calcitonin is derived from Kulchitsky cells, since these might increase or be overactive in such patients. Confirmation, however, must await a larger series.

In conclusion we think that the high plasma calcitonin concentrations found in lung cancer may, at least in some cases, be partially due to the chronic bronchitis that so often accompanies the tumour.

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Requests for reprints should be addressed to: Dr F Galán Galán, Department of Medicine, Hospital Clínico Universitario, Avda Dr Fedriani s/n°, Seville, Spain.

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Department of Medicine, University Hospital School, Avda Dr Fedriani, s/n°, Seville, Spain
FERNANDO GALAN GALAN, MD, senior registrar
JUAN HURTADO, MD, research fellow
RAMON PEREZ CANO, MD, lecturer
MIGUEL GARRIDO PERALTA, MD, professor

Severe metabolic acidosis early in paracetamol poisoning

Serious effects of paracetamol poisoning are held to become evident days after ingestion. We report serious toxicity presenting within hours.

Case report

A 56-year-old housewife swallowed about 75 g of paracetamol. She was admitted 11 hours later deeply unconscious. Examination showed diminished corneal reflexes, absent pain and oculocephalic responses, pallor, vomit around the mouth, tachypnoea, clear chest, trismus, arm flexor spasm, leg flaccidity, and generalised areflexia. Her pulse was irregular (104/min), and blood pressure 110/60 mm Hg with good peripheral perfusion. Stomach washout was performed. Initial assessment included an electrocardiogram, which showed multifocal ventricular extrasystoles and runs of ventricular tachycardia which were abolished by lignocaine. Arterial pH at 12 hours was 6·9, base deficit 25·2, Po_2 16·3 kPa (123·0 mm Hg), Pco_2 2·5 kPa (18·8 mm Hg), and standard bicarbonate concentration 5·1 mmol (mEq)/l (blood gas analyser). Ketostix result was negative and anion gap 34 mmol (mEq), and arterial lactate concentration was 12·9 mmol/l (116·0 mg/100 ml) (normal < 1·2 mmol/l; < 10·8 mg/100 ml).

Rapid infusion of 300 mmol bicarbonate raised the arterial pH to 7·29. Thereafter bicarbonate was infused slowly. By 21 hours after ingestion her acid base state was normal. Plasma paracetamol concentration at 11½ hours was grossly raised at 959 mg/l (estimated half life 11 hours). N-acetylcysteine infusion was begun 13 hours after ingestion and followed a standard regimen.[1] Charcoal haemoperfusion was instituted at 14½ hours and continued for eight and a half hours (see table). A total of 22·8 g of glucuronide and sulphate derivatives of paracetamol plus free paracetamol was excreted in the urine between 12 and 23 hours after ingestion. Screening showed no other drugs. Consciousness gradually returned, and at 24 hours she was fully alert. After the overdose her blood sugar concentration was raised but seven days later the glucose tolerance curve was normal. The liver was only mildly damaged with a peak serum aspartate transaminase value of 258 IU/l at 23 hours and a maximum prothrombin time of 19 s.

Changes in plasma paracetamol concentrations with time after ingestion.

Time (hours)	11½	12½	16	17	18	19	20	21	22	23
Paracetamol (mg/l)	959	918	555	394	288	206	155	144	100	67

Comment

The profound acidosis in this patient may have been attributable to type B lactic acidosis. Neither lactic acidosis nor severe acid base disturbance is recorded in the early stages after paracetamol poisoning. Record *et al*[2] found metabolic acidosis in four out of 28 patients who developed fulminant hepatic failure. In three cases this occurred after paracetamol ingestion, was severe and attributed to lactic