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Disseminated malignant pheochromocytoma: localisation with iodine-131-labelled meta-iodobenzylguanidine

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Abstract

Meta-iodobenzylguanidine, a guanethidine analogue, is a newly synthesised substance capable of imaging the adrenal medulla. In a woman in whom pheochromocytoma had been diagnosed iodine-131-labelled meta-iodobenzylguanidine was given intravenously; gamma-camera images showed bilateral adrenal tumours and uptake corresponding to bone and liver metastases.

¹³¹I-meta-iodobenzylguanidine is effective in localising pheochromocytomas, and the technique is safe, specific, and non-invasive.

Introduction

No agent had been found that was capable of imaging the adrenal medulla until the University of Michigan Medical School synthesised iodine-131-labelled meta-iodobenzylguanidine, a guanethidine analogue, which is structurally similar to noradrenaline and taken up by adrenergic storage vesicles.¹ This correctly localised eight proved pheochromocytomas.² We describe, for the first time in this country, localisation of disseminated malignant pheochromocytoma using this substance, made at Southampton.

Case report

A 52-year-old woman was admitted for investigation of an eight-month history of widespread bone pain, arthralgia, excessive sweating, Raynaud's phenomenon, palpitations, central chest pain, and weight loss (8 kg). She was sweating profusely and was wasted, with peripheral

skin mottling. She had a regular tachycardia (150 beats/min). Blood pressure was 150/130 mm Hg. There were bilateral fundal haemorrhages and exudates. Over the next five weeks she had frequent episodes of palpitations and central chest pain associated with Raynaud's phenomenon in the hands and livedo reticularis in the legs. Blood pressure rose to 240/160 mm Hg, returning to 150/130 mm Hg.

On admission haemoglobin concentration was 9.7 g/dl (normochromic). Biochemical profile was normal except for a raised alkaline phosphatase activity of 768 IU/l, fasting calcium concentration 2.56 mmol/l (10.3 mg/100 ml), and calcitonin concentration 0.1 µg/l (normal <0.08 µg/l). Twenty-four-hour urine total metanephrines were 340 µmol/24 hours (63 mg/24 hours; normal <7 µmol/24 hours (<1.3 mg/24 hours)) (metanephrine 39.5 µmol/24 hours (8 mg/24 hours), normetanephrine 300 µmol/24 hours (55 mg/24 hours)). Radiographs and results of ultrasonography were equivocal, but bone images (technetium-99m-labelled methylenediphosphonate) showed widespread metastases. Liver images (⁹⁹Tc^m-sulphur colloid) showed no focal deposits but suggested a mass above the right kidney. Selective venous sampling was of no help in localising the tumour. Plasma noradrenaline concentration ranged from 5.6 to 12.0 µg/l (normal <1 µg/l). Disseminated malignant pheochromocytoma was diagnosed. Histological confirmation from bone biopsy was not sought because of the risk of pathological fracture. Chemotherapy or radiotherapy was considered not to be indicated. Treatment with phenoxybenzamine 100 mg and propranolol 40 mg, both four times daily, and various analgesics resulted in moderately good control of the pain and cardiovascular symptoms, and she was discharged. Two months later she was readmitted with increased bone pain and postural hypotension.

Meta-iodobenzylguanidine was prepared as described by Wieland *et al.*¹ Animal toxicity studies in 32 Sprague Dawley rats showed no ill effect from 1200 times the imaging dose intended for man. Meta-iodobenzylguanidine was labelled with ¹³¹I and administered intravenously. Gamma-camera images showed bilateral adrenal tumours, widespread bone uptake corresponding to the metastases shown on the bone images, and uptake in the liver corresponding to focal metastases present on repeat liver images (figure).

Discussion

Pheochromocytoma is rare, occurring in about one in 10 000 of the general population. The diagnosis is often made only at necropsy. Of 54 tumours proved at necropsy, 13 had been correctly diagnosed during life.³ Plasma or urinary catecholamine concentrations may be diagnostic, but successful management depends on localising the tumour. Imaging

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(a) Posterior image obtained using ^{131}I -meta-iodobenzylguanidine. (b) Posterior renal image obtained using $^{99\text{m}}\text{Tc}$ -dimercaptosuccinic acid showing displacement and flattening of right upper pole.

procedures such as computed axial tomography may be helpful but are less successful in the 10% of tumours that are extra-adrenal, multiple, or malignant. Use of intravenous contrast and selective venous sampling may be dangerous. In diseases known to be associated with pheochromocytoma demonstration of adrenomedullary abnormalities by a simple non-invasive screening test would be useful.

^{131}I -meta-iodobenzylguanidine can also be used to irradiate tumour tissue selectively; this is analogous to the use of ^{131}I iodide in the treatment of differentiated thyroid malignancy.

Measurement of the uptake of ^{131}I -meta-iodobenzylguanidine in our patient permitted calculation of the tumour radiation dose; a therapeutic dose was subsequently given intravenously as a palliative measure. A similar patient has been treated at the University of Michigan.⁴

Using ^{131}I -meta-iodobenzylguanidine offers a safe, specific, non-invasive procedure for localising pheochromocytoma. Thirty-two such tumours have been correctly identified (Dr Shapiro, University of Michigan Medical School, personal communication). This may prove to be the initial investigation when pheochromocytoma is suspected on clinical and biochemical evidence before more invasive investigations are undertaken.

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Sudden large and periodic changes in heart rate in healthy young men after short periods of exercise

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Abstract

The instantaneous heart rate and respiratory pattern were recorded immediately after brief periods of exercise in 41 healthy male students. Recordings were taken with the subjects both supine and standing. More than half of these subjects showed oscillatory heart changes when recovering supine but not when standing. During these oscillations the heart rate slowed suddenly by more than 30 beats/min; the oscillations had a period of 4 to 8 seconds, and they continued for half to two minutes. The P waves of the electrocardiogram were decreased during the slowing, consistent with increased vagal activity. When these oscillations occurred they each followed the start of an inspiration with the same latency as in respiratory sinus arrhythmia; unlike respiratory sinus arrhythmia, however, they did not occur after every inspiration but varied from 1:1 to 1:3 oscillations:breaths. They were not usually stopped by breath holding but were reduced or abolished by procedures which reduced venous return.

This pattern of oscillations—"vagushalt"—seems to be

different from respiratory sinus arrhythmias, and central venous pressure may contribute to the phenomenon. Although it is not widely recognised, vagushalt is probably very common and possibly its occurrence may change in disease.

Introduction

After brief periods of exercise the instantaneous heart rate often fluctuates in an oscillatory manner while it is returning to the normal resting heart rate.¹⁻³ Wenckebach⁴ described the sudden lengthening of the R-R interval seen during such fluctuations as "bremsungen" (brakings). Kauf¹ observed two patterns of return of the heart rate to normal in subjects recovering in the supine position: the first corresponded to a sinus arrhythmia associated with the breathing cycle, whereas the second showed irregular changes, which he thought were not related to every breath. These latter he called the "vagushalt" phenomenon.

In an earlier study of subjects recovering supine from exercise large "saw toothed" oscillations were observed in most young students examined,² and they were not obviously related to respiration. Davies and Neilson³ reported a similar study but with continuous recording of tidal volumes and with their subjects standing during recovery. They found similar large oscillations of heart rate in five of their 10 subjects but concluded that this was a form of respiratory sinus arrhythmia because there was always a one-to-one relation and a constant phase lag between the breathing and the heart rate cycles.

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