Treatment of mastalgia with bromocriptine: a double-blind cross-over study

Mastalgia is often associated with fibrocystic disease of the breast. Treatments, however, often fail, probably owing to an unsatisfactory understanding of the nature of the condition. In this study we assess the therapeutic efficacy of bromocriptine.

Patients, methods, and results

Severe mastalgia was the dominant feature in 10 women with diffuse fibrocystic disease of the breast as judged by palpation and mammography and verified histologically. One patient (case 1) had galactorrhoea. None had prominent characteristics of the premenstrual syndrome. Mastalgia had been present for from six months to several years. In a double-blind cross-over trial patients were allocated at random to receive either bromocriptine or identical placebo capsules, each for a period of two months, in a dose of one capsule (bromocriptine 2.5 mg or placebo) daily during the first week of each period and thereafter two capsules daily. For one month before the trial and throughout the period of medication the presence and intensity of pain were recorded daily by each patient. They were seen in the outpatient clinic every four weeks. The code was broken at the end of each trial. Serum prolactin concentration was measured before the trial, on the day of cross-over, and on the final day of the trial (normal range 3.0-13.5 µg/l).

During treatment with bromocriptine pain was totally or almost totally relieved in eight patients and in two the pain was much reduced (table). Placebo treatment failed to relieve mastalgia in any patient except one (case 9), in whom the relief during bromocriptine continued while taking placebo. Statistical analysis by Koch's method¹ showed that the relief obtained during bromocriptine therapy was significantly greater ($P < 0.02$) than that during placebo medication, while period effects as well as carry-over effects were absent ($P > 0.05$). Mastalgia reappeared as soon as active medication was stopped, with the exception of the patient in case 9. The breasts became smaller, softer, and less tender during bromocriptine treatment.

The pretrial serum prolactin concentration was slightly raised in three patients and normal in seven. During treatment with bromocriptine these concentrations were significantly lowered ($P < 0.01$, sign test). There were no side effects from placebo. While taking bromocriptine five patients had slight, transitory nausea and dizziness, which is a recognised side effect. Three others had persistent and more pronounced nausea, dizziness, and general malaise.

Comment

The significant beneficial effect of bromocriptine on mastalgia in women with fibrocystic disease of the breast in this controlled study accords with the findings in uncontrolled trials.²⁻⁴ Bromocriptine has also been found effective in premenstrual mastalgia when this is part of the premenstrual syndrome.⁵ But we do not know of any relationship between the premenstrual syndrome and fibrocystic disease. Although three of our patients had slightly raised serum prolactin concentrations, there is no evidence of major disturbances in prolactin secretion in patients with fibrocystic disease and mastalgia,²⁻⁴ and it is uncertain whether prolactin is of any pathogenetic importance. Patients with hyperprolactinaemia do not have mastalgia, probably owing to subnormal oestrogen and progesterone levels caused by prolactin-induced inhibition of gonadal function. It is unproved that

the effect of bromocriptine is mediated through lowering of circulating concentrations of prolactin. This hormone has a mammotropic effect, and possibly lowering the serum prolactin concentration decreases the total stimulatory effect on the breasts and thus stops pain.

We thank Sandoz, Copenhagen, for bromocriptine and the National Pituitary Agency, National Institute of Arthritis, Metabolic and Digestive Diseases, for reagents for prolactin radioimmunoassay.

- ¹ Koch, G G, *Biometrics*, 1972, **28**, 577.
- ² Schulz, K-D, *et al*, *Archiv für Gynäkologie*, 1975, **220**, 83.
- ³ Martin-Comin, J, *et al*, *Obstetrics and Gynecology*, 1976, **48**, 703.
- ⁴ Palmer, B V, and Monteiro, J C M P, *British Medical Journal*, 1971, **1**, 1083.
- ⁵ Andersen, A N, *et al*, *British Journal of Obstetrics and Gynaecology*, 1977, **84**, 370.

(Accepted 15 November 1978)

Department of Surgical Gastroenterology, the Institute of Pathology, and the Department of Diagnostic Radiology, Herlev University Hospital, 2730 Copenhagen, Denmark

M BLICHERT-TOFT, MD, DSC, senior surgeon
A NYBOE ANDERSEN, MD
O B HENRIKSEN, MD, senior pathologist
T MYGIND, MD, DSC, chief of diagnostic radiology

Effect of once-daily atenolol on ambulatory blood pressure

The technique of recording intra-arterial blood pressure in ambulant hypertensive patients throughout complete 24-hour periods^{1,2} has made it possible to study the effects of antihypertensive drugs throughout normal daily activities. The blood pressure follows a 24-hour circadian rhythm with the highest values in the morning and the lowest at night at about 3 am.³ In the early morning there is a rise in pressure, particularly at the time of awakening, continuing up to a peak at about 10 am. This rhythm poses many questions about blood pressure "control" with therapeutic agents, particularly those that are thought to be effective with a single dose. Atenolol, a cardioselective beta-blocking drug with a half life of 6 to 9 hours, is claimed to have such an effect.

Patients, methods, and results

We studied six untreated patients (four men, two women) with confirmed essential hypertension aged 46 to 67 years (mean 59.8). Continuous ambulant intra-arterial blood pressure was measured with a new transducer-perfusion unit² from a brachial artery cannula inserted percutaneously under local anaesthesia. The blood pressure signal and the ECG were recorded on a miniature cassette recorder (Oxford Instruments Ltd). A complete 24-hour recording was carried out in each patient before treatment. The cannula was then removed and each patient was treated with enough atenolol once daily (at 8.30 am) to produce satisfactory clinic blood pressure "control"

Basic data and main results of treatment with bromocriptine and placebo in 10 women with severe mastalgia

Case No	Age (years)	Menstrual cycle	Mastalgia		Intensity of mastalgia*		Serum prolactin concentration (µg/l)		
			Pattern	Location	Bromocriptine (two months)	Placebo (two months)	Pretrial	Bromocriptine	Placebo
1	30	Regular	Cyclical	Unilateral	0	++	6.1	3.2	5.3
2	36	Regular	Cyclical	Unilateral	0	++	11.6	2.6	11.1
3	37	Regular	Cyclical	Bilateral predominance	+	++	6.1	4.0	6.2
4	46	Regular	Constant	Bilateral	0	++	11.7	—	11.4
5	34	Regular	Cyclical	Bilateral	+	++	6.9	3.9	6.3
6	42	Regular	Cyclical	Unilateral	0	++	15.1	2.5	9.9
7	34	Regular	Cyclical	Bilateral predominance	0	++	17.6	—	25.2
8	45	Irregular	Cyclical	Bilateral	0	++	10.2	2.7	7.5
9	49	Irregular	Cyclical	Bilateral	0	0	14.2	7.7	16.7
10	43	Had hysterectomy	Constant	Bilateral	(1st period) 0	(2nd period) ++	20.9	10.3	19.9

* ++ = unchanged; + = appreciably reduced; 0 = total or near total relief of pain.

Mean ambulatory blood pressure (mm Hg) and heart rate in six patients before treatment (—), and after six weeks' treatment with atenolol once daily at 8.30 am (---). Note fall in heart rate throughout the day and lack of effect on nocturnal and early morning blood pressure.

(140/90 mm Hg). Five patients required 100 mg daily and one patient 200 mg. After six weeks the patients were restudied. Four patients agreed to change their medication time from 8.30 am to 11 pm. After a further four weeks these four patients were restudied for a third period of 24 hours. Data were analysed by a hybrid computer system which gave mean systolic and diastolic blood pressure readings and heart rate for each hour of the 24. The data were displayed graphically on a 24-hour axis (figure).

During the pretreatment 24-hour period blood pressure followed the circadian rhythm, as described.³ During the chronic treatment period day-time pressures were substantially reduced but they changed little at night or in the early morning. During the period 6 am to 9 am they were almost identical with the pretreatment pressure. The fall in day-time hourly mean

pressures reached statistical significance (Student's *t* test) but the fall in night-time pressures did not. The pressures of the four patients taking atenolol at 11 pm did not differ from the pressures when they were taking the drug at 8.30 am.

Comment

The circadian rhythm of blood pressure raises many questions about the timing of antihypertensive drug dosage and the effects of traditional regimens. Single measurements in outpatient clinics are unlikely to yield useful information on the effects of drugs on this basic cycle. If treatment aims at lowering blood pressure to a "normal" level (140/90 mm Hg) clearly it is desirable to lower it to that level throughout the 24-hour cycle. Claims for 24-hour control must be examined against this background.

Our study shows that atenolol taken once daily in the morning has a hypotensive effect on day-time blood pressure but little effect on either night-time blood pressure or the early morning rise. This lack of nocturnal and early morning control cannot be related to falling blood concentrations of the drug since the pattern is similar when the dose is given late at night. The mechanism by which beta-blocking drugs lower blood pressure is not clearly understood, but if the early morning rise were due to a sustained alpha-receptor-mediated sympathetic discharge beta-blockers might not be effectual.⁴ This hypothesis remains to be tested.

¹ Bevan, A T, Honour, A J, and Stott, F H, *Clinical Science*, 1969, **36**, 329.

² Millar Craig, M W, Hawes, D, and Whittington, J, *Medical and Biological Engineering*, 1978, **16**, 727.

³ Millar Craig, M W, Bishop, C M, and Raftery, E B, *Lancet*, 1978, **1**, 795.

⁴ Raftery, E B, and Millar Craig, M W, *Proceedings Ghent Symposium on Blood Pressure Variation*. In press.

(Accepted 11 December 1978)

Department of Cardiology, Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex HA1 3UJ

M W MILLAR CRAIG, MB, MRCP, registrar

D KENNY, medical student

STEWART MANN, MA, MRCP, registrar

V BALASUBRAMANIAN, MD, FACC, senior registrar

E B RAFTERY, MD, FRCP, consultant cardiologist

ONE HUNDRED YEARS AGO Hysteria, in its many and varied forms, is one of those reflex nervous phenomena—or, according to Aitkin, "a complex morbid condition of all the cerebral functions"—which the practitioner is generally quick in recognising when it occurs under ordinary circumstances, and presents the usual diagnostic symptoms; but when it assumes exceptional phases and latent forms, such as simulating other diseases, he may either suspect, or doubt, or even altogether fail to recognise, the existence of the real malady under which the patient may be suffering.

Without going into the subject of the theory of reflex action, of cause and effect, or of the various delusions under which some of the subjects of this disease occasionally suffer—with all of which my fellow practitioners are accustomed to deal—I shall at once proceed to give a general outline of a fairly typical case which came under my care a few years ago.

My patient was a lady of about twenty years, bilio-nervous temperament, and slight *physique*. So far as I could ascertain, her general health had been good up to the time of attack. The immediate or exciting cause was the sudden death of a near and dear relative. When I was called in to see the case, I was informed that about three weeks had elapsed since the attack commenced, during which time she had been attended by three other practitioners, all of whom pronounced her to be of unsound mind, and recommended her being removed to an asylum for a time; the chief difficulty about the treatment of her case being her obstinate determination to take neither medicine nor food, as well as her having to be almost constantly restrained from committing acts of violence, indelicacy, and immorality. I found her being forcibly held by three or four attendants; and when I approached and spoke to her, she kicked and spat at me, and refused to either answer questions or obey commands. Her expression was wild and vacant, her pulse weak and quickened; the temperature, defaecation, and micturition were normal, but the last menstruation was deficient. Having obtained full permission to treat her as I thought best, and

knowing how opposed all her relations and friends were to having her taken into an asylum, as well as her own opposition to taking anything *per os*, I determined upon treating her case solely *per rectum* and skin, till it became preferable *per viam naturalem*. Accordingly, I had her placed and held down upon the bed, while I administered a proportionately large dose of the hydrate of chloral, bromide of potassium, and aromatic spirit of ammonia, in milk; this was repeated night and morning, alternating the milk and strong essence of beef, for four or five days; and on or about the third day, I painted over nearly the whole of the dorso-lumbo-sacral regions with the ordinary blistering liquid of the *British Pharmacopoeia*, keeping the surface irritable for some days by applying savine ointment. The vesication was perfect, the amount of serum abundant, and the subsequent counterirritation considerable. The daily dressings and enemata soon became distasteful to her in many ways; and on or about the fifth or sixth day, I found her quieter, more rational, and not offering much opposition to swallowing food and medicine. After this, she made rapid progress, took food naturally and willingly; the vesicated spinal surface was allowed to heal; and she was considered convalescent about the ninth or tenth day. Subsequently, she took walks daily, became courteous and affectionate towards those around her, was sent away on a visit to some relatives at a distance, returned home in about a month, and continued to be in even better health than before the attack.

Now the maxim to be deduced from this case, as representing a class, is just this: that whenever we are called upon to treat a patient who refuses to allow the remedies to be administered in the ordinary way, and that without reasonable cause or excuse, the practitioner should seek to devise an extraordinary way, provided it be likely to aid or accomplish early convalescence; and further that, when the patient is of the gentler sex, and between the periods of puberty and climacteric, and the symptoms are not clearly referable to any other disease, hysteria in some form should be always suspected and sought for. (*British Medical Journal*, 1879.)