and post-implant plasma ACTH levels were measured showed reduced levels. Normal levels were reached in four of the six in whom pituitary implantation was the sole treatment. The attainment of normal plasma ACTH levels (below 80 ng/l) seems a desirable objective, but most patients who have had bilateral adrenalectomy for Cushing's disease and who do not have Nelson's syndrome do have raised levels despite adequate replacement therapy.[20]

The effect of the procedure seems to be long lasting: there were no subsequent relapses, and one patient (case 4) was still in clinical remission with normal plasma ACTH levels 13 years after the pituitary implant. There were few surgical or functional complications of the procedure. Pituitary implant thus compares favourably with the other procedures used for treating Nelson's syndrome.

This series was too small to show which type of radionuclide gave the best results. Each variety of pituitary implant used was followed with at least one good result. We no longer use a combination of ^{90}Y and [198]Au as it is technically difficult to insert accurately. Now we initially assess the size of the tumour with plain radiography, lateral hypocycloidal tomography, and air encephalography. In cases suitable for a pituitary implant ^{90}Y calculated to give a dose of 150 000 rads to the gland periphery is used. If the dorsum sellae is severely eroded there would be inadequate landmarks for implantation; also extension of the subarachnoid space into the pituitary fossa would rule out a pituitary implant because of the danger of a CSF leak, and under these circumstances a transnasal hypophysectomy would be preferred. If the tumour has a large suprasellar extension (>8 mm on air encephalography) the patient would be referred for transfrontal craniotomy. In the event, only two patients were judged more suitable for open surgery.

Two out of four patients showed a clearly normal sella at adrenalectomy, thus showing that it is impossible to exclude the risk of Nelson's syndrome by radiological examination of the fossa. Indeed, one of these patients still had a normal sella at the time of diagnosis of Nelson's syndrome.

From the histopathological viewpoint the present series is the largest so far reported. Nelson et al[2] noted that two of their patients had "chromophobe adenomas," a statement that can be interpreted in the light of our recent findings[8] as meaning active poorly granulated ACTH-secreting tumours. Rivière et al[21] reported a case of Nelson's syndrome with light and electron microscopy findings similar to those described here, but no other biopsies seem to have been reported. Mucoid ACTH-secreting pituitary adenomas are probably central to this syndrome, but the relation of their origin to any presumptive hypothalamic disturbance is still obscure.

References

[1] Nelson, D H, et al, New England Journal of Medicine, 1958, 259, 161.
[2] Nelson, D H, et al, Annals of Internal Medicine, 1960, 52, 560.
[3] Rovit, R L, and Duane, T D, American Journal of Medicine, 1969, 46, 416.
[4] Salassa, R M, et al, Journal of Clinical Endocrinology and Metabolism, 1959, 19, 1523.
[5] Burke, C W, et al, Quarterly Journal of Medicine, 1973, 168, 693.
[6] Joplin, G F, et al, Lancet, 1961, 2, 1277.
[7] Rees, L H, et al, Endocrinology, 1971, 89, 254.
[8] Lewis, P D, and Van Noorden, S, Archives of Pathology, 1972, 94, 119.
[9] Coons, A H, et al, Journal of Experimental Medicine, 1955, 102, 49.
[10] Harsoulis, P, et al, British Medical Journal, 1973, 4, 326.
[11] Cloutier, M D, et al, American Journal of Diseases of Children, 1966, 112, 596.
[12] Schiller, K R F, Proceedings of the Royal Society of Medicine, 1959, 52, 48.
[13] MacKenzie, A D, and McIntosh, H W, American Journal of Surgery, 1965, 110, 135.
[14] Welbourn, R B, et al, British Journal of Surgery, 1971, 58, 1.
[15] Espinoza, A, et al, Acta Endocrinologica (København), 1973, 34, Suppl 173, 34.
[16] Harrison, M T, et al, Proceedings of the Royal Society of Medicine, 1970, 63, 224.
[17] Linfoot, J A, et al, Transactions of the American Clinical and Climatological Association, 1970, 81, 196.
[18] Linfoot, J A, et al, Progress in Atomic Medicine, 1971, 3, 219.
[19] Forrest, A P M, et al, Proceedings of the Royal Society of Medicine, 1970, 53, 616.
[20] Besser, G M, Clinical Endocrinology, 1973, 2, 175.
[21] Rivière, J, et al, Annales d'Endocrinologie, 1975, 36, 359.

Comparison of atenolol and propranolol during insulin-induced hypoglycaemia

S P DEACON,   D BARNETT

Summary

The effects of atenolol, a new beta₁-blocking drug, on pulse rate, sweating, and blood glucose levels during insulin-induced hypoglycaemia were studied in a double-blind crossover trial in eight normal subjects using placebo and propranolol as reference agents. The intensity of induced hypoglycaemia was identical for atenolol, propranolol, and placebo. Propranolol prolonged hypoglycaemia, but atenolol did not. Atenolol may therefore be safe for use in patients receiving insulin.

Introduction

The use of beta-blocking drugs in diabetic patients is contra-indicated because they may intensify hypoglycaemia and prevent the adrenergic signs by which hypoglycaemia is recognised.[1-3] The new selective beta₁-blockers, however, specifically antagonise the actions of catecholamines on the heart and may be free of hypoglycaemic side effects. Atenolol (Tenormin) is a recently developed cardioselective beta-blocker with a combination of pharmacological properties not shown by any other beta-

St James's Hospital, Leeds LS9 7TF
S P DEACON, MB, CHB, house physician
D BARNETT, MRCP, consultant physician

blocker.[1] This trial was designed to study the effects of atenolol during insulin-induced hypoglycaemia.

Subjects and methods

Eight subjects (seven men) aged 22-29 years were studied. All were healthy medical students taking no other medication. None were obese or suffered from respiratory disease. During the trial the subjects took their normal diet and avoided prolonged exercise. Three insulin tolerance tests were performed on each subject at seven-day intervals. Before each test the subjects took either: (a) atenolol 50 mg twice a day, (b) propranolol 80 mg twice a day, or (c) placebo in a double-blind fashion using identical-looking tablets. These were taken for 48 hours with a final dose one hour before the beginning of the test. The subjects fasted overnight and then rested on couches. An indwelling intravenous cannula was inserted and a fasting blood sample taken. An intravenous dose of insulin was then given (0·1 U/kg body weight) and further blood samples taken at 30, 60, 90, and 120 minutes. The pulse rates and degree of sweating (assessed on a scale 0-3) were noted at each of these times. The blood glucose levels were estimated using the GOD-Perid method (Boehringer pack).

Results

Effects on pulse rates and sweating—The resting pulse rates on atenolol and propranolol were similar and showed a decrease of about 12 beats/min from the resting rate on placebo (table I). After hypoglycaemia had been induced the pulse rate in the placebo group rose by 11 beats/min and then returned to resting level by 120 minutes. All the values for the atenolol and propranolol groups were significantly different from those in the placebo group (table II), indicating effective beta-blockade. Pulse rates in the atenolol and propranolol groups were similar apart from the 30-minute value; by this time the atenolol group showed a mean rise in pulse rate of six beats/min. There was no difference in the degree of sweating between placebo, atenolol, or propranolol groups (table III), but the period of sweating was prolonged in the propranolol group.

TABLE I—*Mean (± SD) pulse rates (beats/min)*

Time (min):	0	30	60	90	120
Placebo	65 ± 12·7	76 ± 10·1	69·5 ± 9·3	69 ± 9	65 ± 10·1
Atenolol	53·9 ± 7·1	59·5 ± 10·6	53·6 ± 6·9	51·9 ± 7·5	52·3 ± 6·6
Propranolol	52·5 ± 8·7	49 ± 8·5	48·8 ± 8·7	49·6 ± 3·4	47·5 ± 8·2

TABLE II—*Significance (P values) of differences in pulse rates*

Time (min):	0	30	60	90	120
Placebo v atenolol	<0·05	<0·01	<0·01	<0·001	<0·01
Placebo v propranolol	<0·05	<0·001	<0·001	<0·001	<0·01
Atenolol v propranolol	NS	<0·05	NS	NS	NS

NS = Not significant.

TABLE III—*Sum of sweating scores**

Time (min):	0	30	60	90	120
Placebo	0	7	2	0	0
Atenolol	0	6	3	1	0
Propranolol	0	9	9	5	3

*0 = No sweating.   1 = Clammy.   2 = Mild sweating.   3 = Profuse sweating.

Effects on blood glucose levels—There were no significant differences in the fasting blood glucose levels on placebo, atenolol, or propranolol. The degree of hypoglycaemia induced by equivalent doses of insulin was identical for all three groups (table IV) and represented a 68% fall in blood glucose (expressed as a percentage of the fasting blood glucose level). The rate of recovery of blood glucose levels was similar for placebo and atenolol, and both were significantly different

from propranolol after 60 minutes: placebo v propranolol at 90 and 120 minutes $P < 0·01$; atenolol v propranolol at 90 and 120 minutes $P < 0·05$. By 120 minutes the remaining blood glucose deficit for placebo was 8% and for atenolol 12%, whereas the deficit in the propranolol group was 31%.

TABLE IV—*Mean (± SD) blood glucose levels (mmol/l)*

Time (min):	0	30	60	90	120
Placebo	4·14 ± 0·43	1·31 ± 0·49	2·49 ± 0·63	3·35 ± 0·63	3·79 ± 0·68
Atenolol	4·01 ± 0·12	1·31 ± 0·12	2·79 ± 0·68	3·11 ± 0·2	3·55 ± 0·18
Propranolol	3·98 ± 0·4	1·3 ± 0·57	2·45 ± 0·88	2·4 ± 0·75	2·74 ± 0·82

Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.

Discussion

These results show that propranolol decreases the blood glucose recovery rate after insulin-induced hypoglycaemia and confirm the findings of Abramson et al.[3] Atenolol, however, while providing effective beta-blockade, did not impair blood glucose recovery. This difference is most probably due to the highly selective action of atenolol, which produces only beta$_1$-adrenergic antagonism. Acute hypoglycaemia evokes the secretion of several hormones, including growth hormone,[5] cortisol,[6] adrenaline, and nor-adrenaline,[7] which restore blood glucose levels to normal. The recovery of blood glucose levels is therefore due to several factors, the most important being hepatic glycogenolysis, but increased gluconeogenesis and decreased peripheral glucose uptake play a part. Adrenaline and nor-adrenaline are powerful stimulants of hepatic glycogenolysis[8] by an action on presumed hepatic beta-adrenergic receptors. Non-selective beta-blockers such as propranolol might therefore be expected to prolong hypoglycaemia due to hepatic beta-adrenergic blockade, but cardioselective drugs should be free of this side effect.

Many diabetic patients develop angina pectoris. Although beta-blockers have an established role in the management of angina,[9] [10] their use in diabetic patients with angina is contraindicated. Nevertheless, beta-blockers are occasionally used with caution in diabetic patients with severe angina. This study and other current work[11] suggests that cardioselective beta-blockers are preferable in such cases since they seem to be free of hypoglycaemic side effects.

Atenolol in doses of 50 mg twice a day has been shown to be highly effective in managing severe angina[12] as well as being remarkably free of troublesome side effects.[13] [14] Further work is needed to establish the safe use of atenolol in insulin-dependent diabetics.

References

[1] Kotler, M N, et al, Lancet, 1966, 2, 1389.
[2] Wray, R, and Sutcliffe, S B J, British Medical Journal, 1972, 2, 592.
[3] Abramson, E A, et al, Lancet, 1966, 2, 1386.
[4] Barrett, A M, et al, British Journal of Pharmacology, 1973, 48, 340.
[5] Roth, J, et al, Science, 1963, 140, 987.
[6] Landen, O J, et al, Journal of Endocrinology, 1963, 27, 183.
[7] Goldfien, A, et al, Journal of Endocrinology, 1961, 21, 296.
[8] Hagen, J H, and Hagen, P B, in Actions of Hormones on Molecular Processes, ed G Litwack, p 268. New York, Wiley, 1964.
[9] Gillam, P M S, and Pritchard, B N C, American Journal of Cardiology, 1966, 18, 366.
[10] Master, A M, and Jeffe, H L, American Heart Journal, 1974, 87, 321.
[11] Newman, R, personal communication.
[12] Roy, P, et al, British Medical Journal, 1975, 3, 195.
[13] Hanson, L, et al, British Medical Journal, 1975, 2, 367.
[14] Douglas-Jones, A P, and Cruickshank, J M, British Medical Journal, 1976, 2, 990.