Archives of Disease in Childhood, 1981, **56**, 852–854

Comparison of the intravenous insulin and oral clonidine tolerance tests for growth hormone secretion

THE HEALTH SERVICES HUMAN GROWTH HORMONE COMMITTEE*

SUMMARY The plasma growth hormone response to intravenous insulin was compared with that to oral clonidine in a multicentre trial in 64 patients being investigated for short stature. Either test was judged to give a positive result if the maximum plasma growth hormone concentration was at least 20 mU/l. In 42 pairs of tests concordant results were obtained, 19 being positive and 23 negative. In 12 tests only the response to insulin was positive and 10 tests were positive only for clonidine. Clonidine caused symptoms due to hypotension in some patients but the incidence and severity of side effects varied greatly between centres. It is concluded that clonidine and insulin have similar reliability as tests of growth hormone secretion, but that clonidine may be the safer.

Clonidine is an α-adrenergic drug used therapeutically as a hypotensive agent. In 1975 clonidine was found to stimulate plasma growth hormone (GH) secretion in normal men [1] presumably via a central adrenergic pathway. This led to the drug being tested as a GH stimulus in any child or adolescent who might have GH deficiency. A single oral dose of clonidine produced a large rise of plasma GH in 18 normal subjects and no response in 7 patients suffering from hypopituitarism. In both groups there was a modest fall in blood pressure which did not cause symptoms and the only side effect was drowsiness which persisted for between 1 and 3 hours in all subjects.[2]

The insulin tolerance test (ITT) is currently an essential investigation for patients in the UK who are candidates for GH therapy through the Health Services Human Growth Hormone Committee (HSHGHC). The ITT has been preferred to other tests of GH secretion because we have most experience with it. The hypoglycaemia that occurs during an ITT may cause unpleasant symptoms and is potentially dangerous. In view of the favourable results reported for oral clonidine [2] the HSHGHC decided to compare it with the ITT in a multicentre trial.

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Patients and methods

Sixty-four (16 girls and 48 boys) patients were studied in 11 centres. Their ages ranged from 4·6 to 16·7 years. There was a wide variety of working diagnoses at the time of investigation but the most common was psycho-social deprivation or small/delay, of which there were 28 examples. Fourteen patients were thought to have impaired release of at least one adenohypophyseal hormone.

Patients were either already in hospital or admitted on a 'day care' basis having fasted overnight. The ITT was performed by the intravenous injection of 0·05 to 0·1 units soluble insulin/kg body weight. Blood samples for the measurement of blood glucose and plasma GH were collected at 0, 30, 60, 90, and 120 minutes. A test was considered valid if the plasma glucose concentration fell to a nadir which was less than half that of the fasting level, or was lower than 2·2 mmol/l. The protocol for the oral clonidine test was based on the test performed by Gil-Ad *et al.*[2] A venous cannula was inserted and after 30 minutes clonidine (0·15 mg/m^2) was given by mouth at time 0. Venous blood samples were collected at 0, 30, 60, 90, and 120 minutes and in some cases at −30 and 150 minutes for plasma GH determinations. The two tests were generally carried out within a few weeks of each other but in 6 patients an ITT was performed at least a year before the clonidine test. Hormone measurements were made by the Supraregional Assay Service and all samples from one patient were analysed in the same laboratory. No attempt was made to correct results for inter-laboratory variation but all laboratories used

the same reference standard (IRP for growth hormone, human for immunoassay (66/217)).

A maximum plasma GH concentration of 20 mU/l or more was taken as indicating a normal (positive) GH response to the stimulus and each pair of tests was analysed for concordance.

Results

In 42 of the 64 pairs of tests concordant results were obtained (Table). Half the tests gave positive results and half negative ones. The other 22 tests were evenly divided; 12 gave positive results to the ITT and negative ones with clonidine, 10 gave negative results with the ITT and positive ones with clonidine. The six pairs of tests carried out more than one year apart were similar for the group as a whole: 4 gave concordant results and 2 were discordant.

On average the maximum plasma GH in a positive ITT occurred at 30 or 60 minutes, whereas in a clonidine test the peak GH came at 60 or 90 minutes (Fig. 1). In concordant negative tests there was little change in the mean plasma GH (Fig. 1). In discordant tests (Fig. 2) the mean GH response in the positive test was similar to that observed in the concordant tests, as can be seen if Figs 1 and 2 are compared.

Table *Response to intravenous insulin and oral clonidine tolerance tests in 64 children*

	Intravenous insulin		
	Positive	*Negative*	*Total*
Oral clonidine			
Positive	19	10	29
Negative	12	23	35

Positive indicates that a plasma GH > 20 mU/l was recorded during the test.

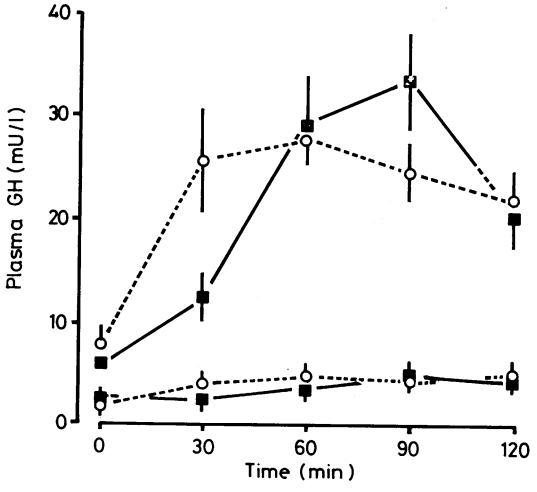

Fig. 1 *Mean (±SEM) plasma GH of patients who had concordant results to intravenous insulin and oral clonidine tolerance tests. Circles indicate the insulin tests and squares the clonidine tests. Nineteen pairs of tests were positive and 23 were negative.*

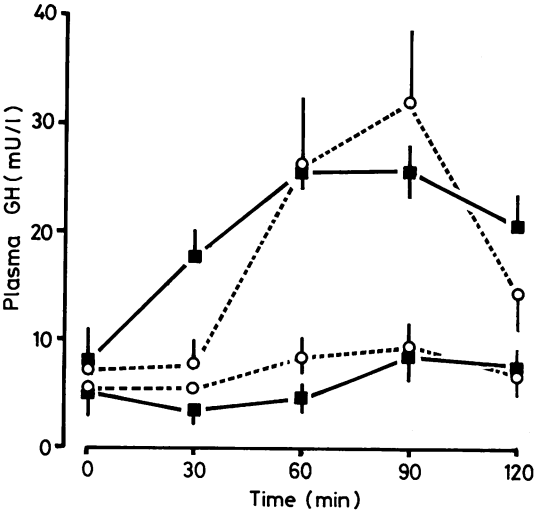

Fig. 2 *Mean (±SEM) plasma GH in intravenous insulin and oral clonidine tests in patients showing discordant results. Squares show the results for 12 patients who had positive responses to insulin and negative responses to clonidine; circles show the results for 10 patients who had positive responses to clonidine and negative responses to insulin.*

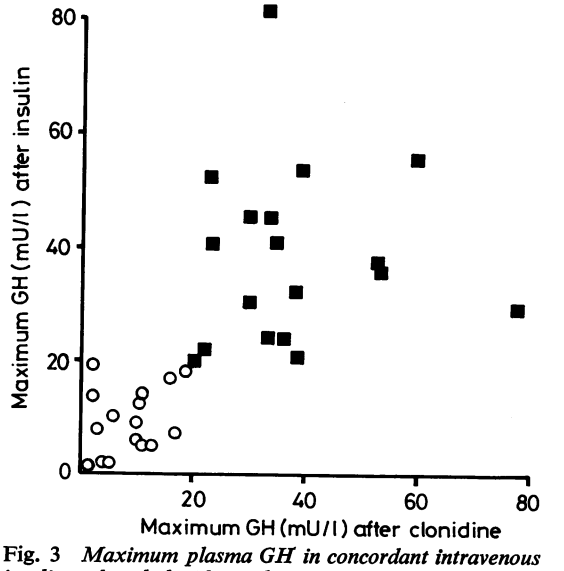

Fig. 3 *Maximum plasma GH in concordant intravenous insulin and oral clonidine tolerance tests. Squares show positive tests and circles negative tests.*

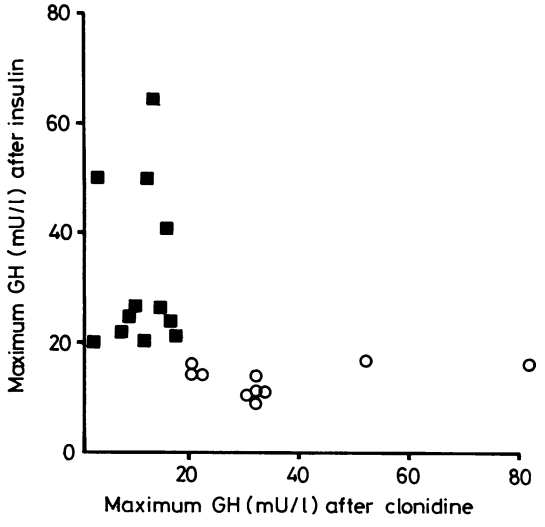

Fig. 4. *Maximum plasma GH in discordant intravenous insulin and oral clonidine tolerance tests. Squares show tests positive to insulin and circles tests positive to clonidine.*

There was a wide variation in the peak plasma GH to insulin or clonidine in both concordant-positive and concordant-negative tests (Fig. 3). In discordant tests there was a wide range of maximum plasma GH results to either insulin or clonidine (Fig. 4). These results show that clonidine is not consistently a more potent stimulus of GH secretion than insulin.

Discussion

This study was designed to mimic normal clinical practice in the UK for the investigation of patients who might have GH deficiency. In this way the efficacy of clonidine as a GH stimulus was compared with the ITT normally used by the HSHGHC in its evaluation of patients.[3] A multicentre design was necessary to obtain sufficient pairs of tests in a short time.

The results indicate that the ITT and oral clonidine test are similarly effective stimuli of GH secretion. If concordance in the two tests is taken as proof of GH deficiency about one-third of the patients were GH deficient. Only half the total study group would have been judged to have normal GH secretion on the basis of one test alone. In other words, each of the two tests had a 25% failure rate, if this is defined as a negative result when a second test showed normal GH secretion.

No one test of GH secretion has been found to have significantly better precision than the ITT[4] and it is customary in some centres to perform at least two different tests before making a biochemical diagnosis of GH deficiency. Exercise may be favoured as a preliminary screen because only one blood sample is taken.[5] The ITT is widely used as the definitive test, despite the possibility of unpleasant side effects and the potential danger from hypoglycaemia. The present results indicate that the oral clonidine test is as effective a diagnostic tool as the ITT, and the side effects from clonidine—hypotension and drowsiness—are less serious than those caused by hypoglycaemia.

Our findings do not confirm the earlier assertion that oral clonidine is a more potent stimulus of GH release than the ITT nor do they confirm the impression that it is uniformly effective.[2]

We thank Mrs E E Lawrence for the help with the collection and collation of the results. The Department of Health and Social Security provided financial support.

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Received 6 November 1980