The effect of nicardipine on glucose and drug-stimulated insulin secretion in normal volunteers

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1 The effect of nicardipine on insulin secretion was examined in two double-blind, randomised, cross-over, placebo-controlled studies in normal volunteers.

2 In the first study, the effect of acute dosing (via an intravenous infusion of 5 mg h⁻¹ for 3 h) on the glucose, insulin, hormonal, and intermediary metabolite responses to an intravenous glucose tolerance test was determined in six healthy male volunteers.

3 In the second study, the glucose, insulin, and C-peptide responses to intravenous tolbutamide (200 mg) was determined in another six male volunteers after oral dosing with nicardipine 30 mg three times daily for 1 week.

4 A relative increase in insulin secretion was the principal finding of the first study. No other response was affected significantly.

5 No significant differences between the nicardipine- and placebo-treated groups were noted in the insulin, glucose, and C-peptide measurements of the second study.

6 In conclusion, treatment with nicardipine does not appear to impair insulin secretion in response either to an intravenous glucose load or intravenously administered tolbutamide.

Keywords insulin secretion nicardipine volunteers

Introduction

It has been well established by *in vitro* studies (Grodsky & Bennett, 1966; Hellman, 1975) that extracellular calcium is essential for the release of insulin. With the development of calcium entry blocking drugs for the treatment of cardiovascular disease, it was recognized that a potential side effect might be impairment of glucose tolerance by inhibition of insulin release. This would be of particular importance as a substantial number of diabetic patients develop cardiovascular disease (Harrower, 1977).

Many studies have been performed with calcium entry blockers to evaluate the effects on glucose and insulin, both in normal volunteers and in patients (Andersson & Röjdmärk, 1981; Donnelly & Harrower, 1980; Charles *et al.*, 1981; Giugliano *et al.*, 1980; De Marinis & Barbarino, 1980; Semple *et al.*, 1983), but the reported results were conflicting. Because a number of studies with verapamil and nifedipine have

provided evidence that insulin secretion might be impaired, it seemed essential to establish whether or not nicardipine had any effect on insulin secretion.

Methods

Two studies were performed in the Clinical Pharmacology Unit at Syntex Research, Scotland. Both studies were approved by an independent Ethics Review Committee and were conducted in accordance with the conditions of the Declaration of Helsinki.

Study 1

Six normal healthy male volunteers (average age, 22.3 years; average weight, 72.6 kg) participated

Table 1 Group mean results for biochemical values (Study 1)

	Pre-dose	60 min	70 min	80 min	90 min	100 min	110 min	120 min	135 min	150 min	165 min	180 min	c.v. †
Glucose (mmol l ⁻¹)													
Placebo	5.2	5.2	13.2	10.6	8.6	7.5	6.6	6.0	5.4	5.0	5.0	4.7	
NIC HCl	5.1	5.3	12.9	10.8	9.4	8.3	7.5	6.8	6.1	5.4	5.2	5.0	±2.2%
Insulin (µu ml ⁻¹)													
Placebo	11.0	9.5	30.2	19.5	16.2	17.0	17.0	15.2	14.0	14.0	12.0	11.5	
NIC HCl	11.0	11.2	31.5	21.8	23.0	23.2	22.0	20.0	16.8	15.0	12.0	11.5	±8.9%
Glucose/Insulin ratio†													
Placebo	0.485	0.549	0.461	0.718	1.142	0.437	0.390	0.456	0.424	0.364	0.438	0.415	
NIC HCl	0.482	0.481	0.553	0.682	0.415	0.360	0.359	0.377	0.404	0.377	0.457	0.445	
C-peptide (pmol ml ⁻¹)													
Placebo	0.26	0.25	0.69	0.63	0.56	0.58	0.56	0.51	0.44	0.40	0.34	0.31	
NIC HCl	0.25	0.23	0.59	0.62	0.57	0.57	0.55	0.55	0.48	0.45	0.34	0.33	±8.1%
β-Hydroxybutyrate (mmol l ⁻¹)‡													
Placebo	0.09	0.11	0.13	0.10	0.07	0.06	0.05	0.05	0.05	0.05	0.05	0.06	
NIC HCl	0.20	0.23	0.24	0.17	0.11	0.08	0.05	0.05	0.05	0.06	0.07	0.11	±2%
Acetoacetate (mmol l ⁻¹)‡													
Placebo	0.03	0.04	0.03	0.03	0.03	0.02	0.03	0.03	0.03	0.03	0.03	0.03	
NIC HCl	0.05	0.06	0.05	0.05	0.04	0.05	0.03	0.04	0.03	0.03	0.04	0.04	±14.1%
Lactate (mmol l ⁻¹)													
Placebo	0.92	0.90	1.11	1.18	0.96	1.21	1.16	1.13	0.97	0.94	0.89	0.87	
NIC HCl	1.21	0.94	1.10	1.10	1.23	1.25	1.23	1.20	1.11	1.02	0.96	0.89	±4.4%
	***	***		*		**	**	*	3	*	***	***	***

Pyruvate (mmol l ⁻¹)	Placebo	0.055	0.048	0.064	0.061	0.078	0.076	0.080	0.070	0.069	0.060	0.056	0.047
	NIC HCl	0.073	0.051	0.066	0.077	0.073	0.088	0.091	0.071	0.088	0.062	0.060	0.048 ± 14.9%
Glycerol (mmol l ⁻¹)	Placebo	0.059	0.094	0.162	0.112	0.088	0.074	0.084	0.074	0.063	0.059	0.071	0.063
	NIC HCl	0.091 ⁴	0.095	0.112	0.080	0.081	0.069	0.069	0.064	0.062	0.060	0.073	0.079 ± 6.7%
Alanine (mmol l ⁻¹)	Placebo	0.37	0.34	0.35	0.35	0.35	0.36	0.36	0.37	0.38	0.38	0.38	0.38
	NIC HCl	0.40	0.36	0.37	0.37	0.37	0.37	0.38	0.37	0.37 [*]	0.36 ⁵	0.36	0.35 ± 4.7%
Growth hormone (ng ml ⁻¹) [‡]	Placebo	5.6	4.1	3.8	3.7	3.6	3.3	3.1	2.9	2.8	3.1	4.6	7.4
	NIC HCl	7.5	4.4	3.6	3.4	3.2	3.0	2.8	2.7	2.8	3.1	3.0	3.7 ± 10.9%
Cortisol (nmol ml ⁻¹)	Placebo	354.2	294.3	305.8	311.2	270.8	265.7	274.8	273.2	275.3	269.8	253.8	260.5
	NIC HCl	415.7	303.3	281.0	250.2	243.0	254.2	263.8	266.3	299.3	288.2	287.3	325.5 ± 7.1%
Glucagon N-gli (pg ml ⁻¹)	Placebo	112.5	108.0	120.8	100.8	108.3	102.5	101.7	98.3	95.8	95.8	106.7	102.5
	NIC HCl	105.8	94.2	92.5	90.8	94.2	94.2	88.3	91.7	86.7	90.0	84.2	101.7 ± 7.5%
Glucagon C-gli (pg ml ⁻¹)	Placebo	95.0	88.0	112.5	88.3	86.7	80.0	85.0	80.8	95.8	89.2	105.0	94.2
	NIC HCl	94.2	85.8	89.2	73.3	87.5	95.8	76.7	81.7	83.3	83.3	78.3	100.8 ± 7.5%

* Change from baseline value after nicardipine statistically significantly different from change from baseline value after placebo: * $P < 0.05$, ** $P < 0.025$, *** $P < 0.001$, 1 $P = 0.067$, 2 $P = 0.059$, 3 $P = 0.051$, 4 $P = 0.073$, 5 $P = 0.077$.

† Between-batch coefficient of variation for assay.

‡ Statistical analysis by nonparametric methods.

in a double-blind, randomised, cross-over, placebo-controlled study involving the intravenous infusion of either nicardipine (5 mg h^{-1}) or placebo (saline) for 3 h on each of two separate study days, with a wash-out period of 7 days between study periods. An intravenous glucose load of 0.33 g kg^{-1} was administered 1 h after the start of the infusion. Blood was removed before starting the infusion, before the injection of the glucose, at 10 min intervals for the first hour and at 15 min intervals for the second hour after injection of the glucose. These blood samples subsequently were analysed for glucose, insulin, C-peptide, cortisol, growth hormone, glucagon, β -hydroxybutyrate, acetoacetate, lactate, pyruvate, glycerol and alanine. Blood pressure and heart rate also were monitored.

Study 2

Six healthy male volunteers (average age, 22.5 years; average weight, 77.5 kg) participated in a double-blind, randomised, cross-over, placebo-controlled study. Each volunteer received, in two study phases separated by a wash-out period of at least 7 days, nicardipine (30 mg) or placebo three times daily for 7 days with a single dose on the eighth day. One hour after this last dose an intravenous injection of tolbutamide (200 mg) was administered; blood for subsequent analyses of glucose, insulin, and C-peptide was removed before dosing with nicardipine and immediately before and 1, 2, 4, 6, 8, 10 and 15 min after injection of tolbutamide.

Biochemical analyses

The coefficients of variation for the measurements in study 1 are given in Table 1.

Glucose

Glucose was measured by a glucose oxidase method using a Beckman Glucose Analyser II and Beckman Reagents.

Hormones

Growth hormone, cortisol, insulin, and C-peptide were assayed by standard radio-immunoassays using kits supplied by I.R.E. U.K. Limited. All of these methods used ^{125}I -labelled antigens; the radioactivity was determined in Nuclear Enterprises NE1600 counter.

Assays of immunoreactive glucagon were performed by Professor K. Buchanan, Belfast.

Metabolites

The metabolites were analysed by methods adapted to the Rotachem 11A Centrifugal Fast Analyser using appropriate kinetic rate programmes.

Statistical methods

Parametric analysis of variance of the two-period cross-over design (Hills & Armitage, 1979) was employed for all biochemical measurements except β -hydroxybutyrate, growth hormone, and acetoacetate which, because of apparent violations of the parametric model, were analysed by non-parametric statistical methods (Grizzle, 1965).

Results

Study 1

Mean results for glucose, insulin, glucose/insulin ratio, C-peptide, and those hormones and metabolites that were measured are summarised in Table 1. For glucose, insulin, glucose/insulin ratio, β -hydroxybutyrate, lactate and alanine, there were statistically significant differences between changes from baseline values after nicardipine compared with changes from baseline values after placebo. The statistically significant differences shown for these measurements (other than those for glucose and insulin) were thought not to be clinically relevant, as the actual differences were small compared with known biological fluctuations and the coefficient of variation of the assays.

When area under the curve (AUC) was calculated for glucose and insulin (Table 2, Figure 1), five of the six volunteers had a higher AUC for glucose after nicardipine, but the group mean result was not statistically significantly different from that obtained with placebo.

In all six subjects, the AUC for insulin following the nicardipine infusion was greater than the AUC following placebo, and the group mean result after nicardipine was significantly greater than that obtained with placebo ($P < 0.05$).

Study 2

The results for glucose, insulin, and C-peptide are summarised in Table 3. There were no statistically

Table 2 Calculated area under the curve (AUC) for glucose and insulin (Study 1)

Volunteer	Glucose ($\text{mmol l}^{-1} \text{ min}$)		Insulin ($\mu\text{u ml}^{-1} \text{ min}$)	
	Placebo	Nicardipine	Placebo	Nicardipine
1 (1)	928.2	977.2	2037.5	2277.5
1 (2)	668.0	798.8	1595.0	1942.5
1 (3)	899.0	915.8	1902.5	2205.0
1 (4)	987.5	829.8	2342.5	2645.0
1 (5)	804.2	906.0	1902.5	2680.0
1 (6)	707.5	911.5	1750.0	1837.5
Mean	832.4	889.8	1922.0	2265.0*
s.d.	127.4	64.7	256.0	348.0

* Nicardipine significantly different from placebo ($P < 0.05$).

Figure 1 The glucose (○) and insulin (▲) response to an intravenous glucose load (0.33 g kg^{-1}) after infusion of nicardipine (—) and placebo (---).

Table 3 Group means results for biochemical values (Study 2)

	<i>Pre-dose</i>	<i>60 min</i>	<i>61 min</i>	<i>62 min</i>	<i>64 min</i>	<i>66 min</i>	<i>68 min</i>	<i>70 min</i>	<i>75 min</i>
Glucose (mmol l⁻¹)									
Placebo									
Mean	4.9	4.5	4.5	4.7	4.6	4.5	4.4	4.2	3.9*
s.d.	0.4	0.4	0.2	0.2	0.1	0.1	0.3	0.4	0.4
Nicardipine									
Mean	4.8	4.8	4.9	4.9	4.7	4.8	4.6	4.6	4.3*
s.d.	0.2	0.3	0.3	0.3	0.5	0.2	0.3	0.3	0.3
Insulin (μU ml⁻¹)									
Placebo									
Mean	10.7	11.8	22.0*	42.3**	56.0**	41.8**	27.0**	20.2**	15.0
s.d.	2.2	2.3	19.8	33.7	21.1	13.7	9.5	6.6	4.3
Nicardipine									
Mean	8.3	11.0	55.5**	74.0**	46.8**	28.7**	18.2**	16.0*	14.2
s.d.	1.4	2.8	23.9	21.7	10.0	10.3	6.2	5.3	4.4
			# #	# #					
C-Peptide (pmol ml⁻¹)									
Placebo									
Mean	0.58	0.54	0.88**	1.05**	1.36**	1.26**	1.18**	1.02**	0.86**
s.d.	0.10	0.07	0.60	0.53	0.37	0.32	0.30	0.21	0.10
Nicardipine									
Mean	0.50	0.47	1.02**	1.35**	1.21**	1.02**	0.91**	0.80**	0.75**
s.d.	0.10	0.11	0.33	0.35	0.32	0.21	0.17	0.15	0.13
			# #	# #					

Comparison with 60 min value: * $P < 0.05$, ** $P < 0.01$.

Comparison between nicardipine and placebo (change from 60 min): # $P < 0.05$, # # $P < 0.01$.

Table 4 Calculated area under the curve (AUC) for glucose and insulin (Study 2)

<i>Volunteer</i>	<i>Glucose† (mmol l⁻¹ min)</i>		<i>Insulin (μU ml⁻¹ min)</i>	
	<i>Placebo</i>	<i>Nicardipine</i>	<i>Placebo</i>	<i>Nicardipine</i>
2 (1)	-7.55	-3.35	513.5	348.0
2 (2)	-4.85	-2.70	421.5	413.0
2 (3)	-3.40	-1.65	274.5	276.0
2 (4)	-1.00	-3.20	386.5	562.0
2 (5)	-0.50	-4.50	521.0	538.0
2 (6)	-6.50	-4.95	578.0	567.5
Mean	-3.97	-3.39	449.2	450.8
s.d.	2.87	1.20	110.5	123.4

† Glucose AUC calculated as area below the baseline and corrected for difference between pre-tolbutamide values. (-) sign indicates reduction from baseline.

There were no significant differences between the mean results.

significant differences between nicardipine and placebo for fasting pre-dose glucose, insulin, and C-peptide values on the final day. After injection of tolbutamide, there were significant increases in insulin and C-peptide and a reduction in glucose. After nicardipine, the mean insulin and C-peptide levels were significantly higher compared with the mean levels after placebo 1 and 2 min after i.v.

tolbutamide ($P < 0.05$). After a pre-tolbutamide injection difference (0.3 mmol) between nicardipine and placebo was taken into account, reduction in mean plasma glucose levels was similar.

A corrected AUC for glucose after i.v. tolbutamide was calculated to account for a 0.3 mmol difference between pre-tolbutamide

Figure 2 The glucose (○) and insulin (▲) response to intravenous tolbutamide (200 mg) after nicardipine 30 mg (—) and placebo (---).

glucose levels (Table 4, Figure 2). The corrected glucose AUC after nicardipine was not significantly different from that after placebo ($P > 0.05$). Comparison of the AUCs, showed that the overall insulin response to i.v. tolbutamide did not differ significantly between nicardipine and placebo.

Discussion

In the literature, conflicting reports exist of the effects of calcium entry blockers on insulin secretion in both normal subjects and patients with diabetes mellitus. From a study with intravenous infusions of verapamil, De Marinis & Barbarino (1980) reported impaired glucose

tolerance and a reduction in insulin secretion. However, a chronic oral dose study with the same compound (Semple *et al.*, 1983) demonstrated no effect in nondiabetic subjects with angina pectoris. Another study with verapamil (Andersson & Röjdmarm, 1981) demonstrated that acute intravenous and chronic oral dosing for 7 days did not impair insulin secretion in either normal or diabetic subjects and appeared to improve glucose tolerance in the latter group.

A study with oral nifedipine given for 3 days demonstrated impaired glucose tolerance with a reduction in insulin secretion in nondiabetic subjects (Charles *et al.*, 1981). Further, Giugliano *et al.* (1980) showed that nifedipine given for 10 days impaired insulin secretion without reducing glucose tolerance in normal subjects. In diabetic subjects insulin secretion was impaired and glucose tolerance was reduced. Donnelly & Harrower (1980) could find no effect on glucose tolerance or insulin secretion in diabetic and nondiabetic patients when nifedipine was used either in single doses or for 28 days.

These conflicting reports and recognition that different calcium entry blocking drugs may act at different cellular sites (Braunwald, 1982) made it important to establish whether or not nicardipine affected either glucose tolerance or insulin secretion. The two studies reported in this paper were designed to establish the role of nicardipine and to provide preliminary evidence of safety in order to allow further studies in diabetic and nondiabetic subjects.

An i.v. infusion of nicardipine was used in the first study. It was felt that acute dosing was appropriate as calcium is essential for the release of stored hormone rather than for synthesis of the hormone; any effect of the drug would therefore be more apparent using the i.v. route. The results demonstrated that nicardipine did not impair, and indeed increased, insulin secretion. This increased secretion of insulin, however, did not appear to result in an increased clearance of

glucose; indeed, there is some evidence (by comparison of the AUCs for glucose) that glucose clearance might be moderately impaired. A possible explanation for this might be an impairment of the peripheral action of insulin, as has been shown *in vitro* by Ishibashi & Kutso (1982).

The second study was designed to establish whether or not chronic oral dosing with nicardipine might impair the action of an oral hypoglycaemic drug. Intravenous tolbutamide was chosen to avoid the marked variability of absorption seen after oral dosing with tolbutamide (Melander *et al.*, 1978). The dose of 200 mg of tolbutamide was selected because previous workers (Ganda *et al.*, 1975; Tötterman & Groop, 1982) had demonstrated that a significant short-term insulin response could be obtained with this dose without risk of inducing hypoglycaemia. The results of this study confirmed that intravenous tolbutamide 200 mg produced a significant insulin response over 15 min. Although the time to peak response varied in the nicardipine and placebo groups, the total response, as assessed by the AUC for insulin was not different. Thus, the insulin release provoked by a hypoglycaemia-producing drug was not reduced by chronic dosing with nicardipine.

In conclusion, these studies in normal subjects indicate that nicardipine does not impair insulin release in response to either an intravenous glucose load or intravenously administered tolbutamide. Both the possibility of interference with the peripheral action of insulin and the effect of chronic dosing of nicardipine in diabetic subjects are to be determined in future studies.

We wish to thank Professor K. Buchanan (Belfast) for performing the glucagon assays, Mr K. F. Yee for performing the statistical analysis, Miss Alison Steward for typing the manuscript, and the volunteers who participated in the studies.

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