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SHORT COMMUNICATION

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Effect of atenolol on QTc interval lengthening during hypoglycaemia in type 1 diabetes

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Abstract *Aims/hypothesis:* Hypoglycaemia is associated with heart rate-corrected QT (QTc) interval lengthening on the ECG; this may be important in the pathogenesis of sudden overnight death in young people with diabetes. Since hypoglycaemic QTc lengthening appears to be mediated through the sympathoadrenal response, we tested the hypothesis that beta$_1$-blockade will prevent these changes in type 1 diabetic patients and so provide a potential therapeutic intervention. *Methods:* We studied eight type 1 diabetic adults without cardiovascular or renal complications. Similar hypoglycaemic clamp studies were performed on two occasions, at least 4 weeks apart, but immediately before one visit subjects received atenolol 100 mg daily for 7 days. Following a 60-min euglycaemic (5 mmol/l) period, blood glucose was lowered over 30 min to 2.5 mmol/l, and held for 60 min. High-resolution ECG was recorded at baseline and at 0, 30 and 60 min during each glycaemic plateau. QT interval was measured using a semiautomated tangent method and QTc was derived from QT using the Fridericia formula. *Results:* Mean (SD) baseline QTc was similar at both visits: control 391 (30) ms, post-atenolol 386 (34) ms; (p=0.33). Without atenolol pretreatment, QTc lengthened during hypoglycaemia to a maximum of 448 (34) ms (p<0.001). On atenolol, QTc lengthening was significantly reduced (peak QTc 413 (27) ms; p=0.004 vs control visit). *Conclusions/interpretation:* Hypoglycaemic QTc lengthening is blunted by atenolol in patients with type 1 diabetes. Selective beta$_1$-blockade may help prevent sudden death, if we can identify those at high risk.

Keywords Atenolol · Hypoglycaemia · QT interval · Sudden death

Abbreviations Ca^{2+}: calcium · DBP: diastolic blood pressure · K^+: potassium · Mg^{2+}: magnesium · MAP: mean arterial pressure · RMS: root mean square · SBP: systolic blood pressure

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Introduction

Hypoglycaemia has been implicated in the syndrome of sudden overnight death in young diabetic patients [1]. We have previously reported lengthening of rate-corrected QT (QTc) interval on the ECG during experimental [2] and clinical [3] hypoglycaemia in type 1 diabetic subjects, and proposed hypoglycaemia as a cause of the acquired long QT syndrome [4]. Since QTc prolongation predicts ventricular arrhythmias [4], we have proposed this as a mechanism of mortality [5].

Adrenaline (epinephrine) infusion causes QTc lengthening [6], and similar changes during hypoglycaemia are associated with sympathoadrenal activation [2, 4]. We have previously shown that short-term administration of the selective β_1-adrenergic blocking agent atenolol largely prevents hypoglycaemic QTc lengthening in non-diabetic subjects [4]. The aim of the present study was to investigate

the effect of atenolol on QTc prolongation during experimental hypoglycaemia in adults with type 1 diabetes.

Subjects, materials and methods

We studied eight type 1 diabetic participants (seven male, one female) without known cardiovascular disease, nephropathy or autonomic neuropathy; none were taking medication other than insulin. All participants gave written informed consent, and the local research ethics committee approved the study.

Experimental protocol We studied participants who had shown QTc lengthening during previous experimental hypoglycaemia [2]. They were invited to undergo a similar hypoglycaemic clamp at least 4 weeks later; before this second visit, subjects took atenolol 100 mg daily for 7 days up to and including the study day. The visit order was therefore not random.

The experimental protocol was as previously described [2]. Participants attended at 08:00 hours; insulin (Human Actrapid; Novo Nordisk Pharmaceuticals, Crawley, UK) was then infused to maintain blood glucose between 5 and 10 mmol/l. The clamp began at 12:30 hours. Arterialised venous blood glucose was initially held at around 5 mmol/l for 60 min, lowered over 30 min to a target nadir of 2.5 mmol/l, then held at 2.5 mmol/l for 60 min. Measurements, made every 30 min during each glucose plateau, consisted of QTc interval, heart rate, blood pressure, finger tremor, sweat production, plasma potassium (K^+), albumin-adjusted calcium (Ca^{2+}) and magnesium (Mg^{2+}). Plasma catecholamines were measured at baseline, at the end of the euglycaemic period, and after 30 min and 60 min of hypoglycaemia. Plasma free insulin concentration was measured at the end of each glucose plateau.

Measurement of QTc interval Signal-averaged ECG recordings were made using a custom-built high-resolution system with a tangent method applied for semiautomated QTc interval measurement [7]. The Fridericia cube root formula was used to correct QT for heart rate [8].

Biochemical analyses Blood glucose, HbA_{1c}, plasma potassium, magnesium, calcium, adrenaline (epinephrine), noradrenaline (norepinephrine) and free insulin were determined as described previously [2]. Inter- and intra-assay coefficients of variation were 9.9 and 8.5%, respectively, (adrenaline [epinephrine]), 3.9 and 1.2% (noradrenaline [norepinephrine]) and 5.8 and <5% (insulin).

Statistics Data were assessed for normality of distribution using the Shapiro–Wilk test. Comparisons not involving time were made using the paired *t*-test or Wilcoxon matched pairs test as appropriate. Differences in hypoglycaemic responses between the two visits were evaluated using repeated measures ANOVA, followed by the paired *t*-test or Wilcoxon test. The relationship between adrenaline (epinephrine) response and QTc was examined using linear regression analysis. Results are expressed as means ±SD unless otherwise stated, and $p<0.05$ was judged significant. Analyses were performed using SPSS version 10.0 (SPSS for Windows; SPSS, Chicago, IL, USA).

Results

Participant characteristics Subjects were aged 35±8 years, had a duration of diabetes of 15±6 years and a BMI of 24±3 kg/m^2. Glycaemic control was similar at both visits (HbA_{1c} 9.0±1.0% [control visit] vs 9.0±1.0% [atenolol visit], $p=0.86$).

Table 1 Physiological responses

	Baseline	Eug 0	Eug 30	Eug 60	Hypo 0	Hypo 30	Hypo 60
Heart rate (beats/min)							
Control	64±7	65±6	66±5	64±7	72±7	74±6	74±5
Atenolol[a]	55±6	54±6	53±8	53±5	55±6	57±10	57±4
SBP (mmHg)							
Control	117±7	117±7	120±6	118±7	119±6	120±7	121±10
Atenolol	113±8	110±9	113±10	107±8	109±9	109±12	111±14
DBP (mmHg)							
Control	70±6	71±7	71±5	72±5	71±5	67±7	70±7
Atenolol	65±9	66±9	64±11	64±9	64±9	63±7	64±8
MAP (mmHg)							
Control	89±6	88±5	89±4	89±5	90±5	88±6	90±8
Atenolol	83±7	81±12	82±9	81±9	81±8	81±10	82±9
Sweat (g·min^{-1}·m^{-2})							
Control	25.2±12	20.2±9.4	21.2±12.1	29.8±16.0	50.4±75.3	169.4±201.4	126.0±180.8
Atenolol	22.6±9	21.1±9.6	27.1±22.4	23.6±15.9	30.6±16.2	131.9±128.9	136.6±149.8
Tremor (RMS V/s)							
Control	0.11±0.03	0.12±0.03	0.13±0.03	0.12±0.04	0.15±0.05	0.22±0.06	0.18±0.06
Atenolol[b]	0.09±0.02	0.11±0.0.05	0.12±0.03	0.12±0.04	0.14±0.05	0.12±0.06	0.13±0.04

Columns denote 0, 30 and 60 min of euglycaemia (Eug 0, Eug 30 and Eug 60) and 0, 30 and 60 min of hypoglycaemia (Hypo 0, Hypo 30 and Hypo 60)
Data are means±SD
SBP systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *RMS* root mean square
[a] $F=3.27$, $p=0.006$ vs control visit; [b] $F=3.97$, $p=0.012$ vs control

Biochemical Blood glucose concentrations were comparable at both visits (data not shown).

Plasma insulin concentrations were similar at steady-state euglycaemia and hypoglycaemia during the control (80±5 vs 75±6 mU/l, p=0.15) and atenolol (87±7 vs 83±5 mU/l, p=0.43) visits. There was no difference between insulin concentrations during the control and atenolol visits (euglycaemia, p=0.45; hypoglycaemia, p=0.32).

Plasma potassium was similar at baseline (atenolol, 3.9±0.2 mmol/l; control, 3.9±0.2 mmol/l; p=0.59). Potassium fell during both visits, with no differences between visits (F=1.25, p=0.30). After 60 min of euglycaemia, plasma K^+ had fallen during the control visit by 0.5±0.1 mmol/l and by 0.4±0.2 mmol/l during the atenolol visit (p=0.11). During hypoglycaemia plasma K^+ fell by a further 0.3±0.2 mmol/l (control) and by 0.2±0.2 mmol/l (atenolol) (p=0.50).

Plasma Ca^{2+} and Mg^{2+} were similar during all measurements at baseline and remained unchanged during both visits (data not shown).

Basal plasma adrenaline (epinephrine) and noradrenaline (norepinephrine) concentrations were comparable at both visits (adrenaline [epinephrine], p=0.46; noradrenaline [norepinephrine], p=0.67). During hypoglycaemia, noradrenaline (norepinephrine) responses did not differ between visits (F=0.085, p=0.90), and although, as expected, adrenaline (epinephrine) responses tended to be augmented following pretreatment with atenolol (peak adrenaline [epinephrine] concentration 3.41±1.07 vs 2.80±0.63 nmol/l during the control visit), these were not significantly greater than control responses (F=0.42, p=0.55). There was a trend towards a correlation between peak adrenaline (epinephrine) response and QTc lengthening during the control visit (r=0.62, p=0.10).

Physiological measurements Physiological responses are shown in Table 1. Baseline heart rate was reduced by atenolol (p=0.03). Heart rate increased during hypoglycaemia in the control visit (F=9.7, p<0.001), but this was prevented by atenolol.

Baseline finger tremor (p=0.18) and rates of sweating (p=0.67) were similar with and without atenolol. At each visit, there was a similar increase in sweat production during hypoglycaemia (F=0.15, p=0.80); tremor increases were greater during the control visit (F=3.97, p=0.012).

QTc interval (Fig. 1) Baseline QTc was similar at each visit (control 391±30 ms, atenolol 386±34 ms), (p=0.33). During euglycaemia, QTc increased to a similar extent, with (11±6 ms) and without (16±14 ms) atenolol (p=0.43). However, during hypoglycaemia, QTc lengthening was blunted by atenolol, with peak increases from baseline of 27±9 ms to 57±17 ms during the control visit (F=4.46, p<0.001; Fig. 1b). Maximum QTc duration was greater without (448±34 ms) than with atenolol (413±27 ms) (p=0.004).

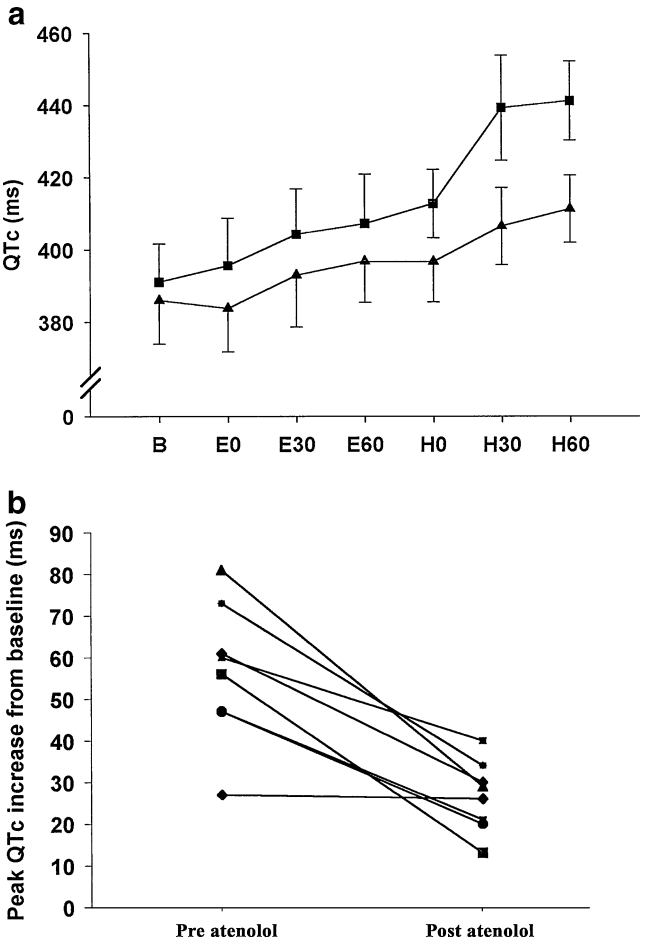

Fig. 1 **a** Effect of hypoglycaemia on QTc interval. Mean±SD QTc at baseline (**b**) and after 0, 30 and 60 min of euglycaemia (E0, E30 and E60) and after 0, 30 and 60 min of hypoglycaemia (H0, H30 and H60). *Squares*, before atenolol; *triangles*, after atenolol. **b** Individual maximal QTc increases during hypoglycaemia. *Triangles*, pre-atenolol; *squares*, post atenolol

Discussion

In this study, the selective beta$_1$-adrenergic antagonist atenolol significantly reduced hypoglycaemic QTc lengthening in type 1 diabetic adults. These agents therefore might offer a potential therapeutic approach, with benefits analogous to the reduced incidence of ventricular arrhythmia in congenital long QT syndrome patients taking beta-adrenoceptor-blocking therapy [9].

Our data support earlier work implicating the sympathoadrenal response as the mechanism underlying hypoglycaemia-induced QTc prolongation. Adrenaline (epinephrine) infusion lengthens QTc in non-diabetic subjects [6], and we have previously shown that QTc lengthening is related to the rise in circulating adrenaline (epinephrine) during hypoglycaemia in individuals with type 1 diabetes [2]. The absence of a significant relationship in the control visit between increases in adrenaline (epinephrine) and QTc is probably explained by the small numbers.

The observed decline in serum potassium is due to a combination of hyperinsulinaemia and sympathoadrenal activation during hypoglycaemia [10], the latter reflecting peripheral $beta_2$-adrenoceptor stimulation [11]. Although atenolol abolished increases in tremor and heart rate during hypoglycaemia, increases in QTc were only partially prevented. This is probably explained by the effect of hyperinsulinaemic hypokalaemia on QTc, independent of hypoglycaemia [2, 4]. There was a trend towards an attenuated fall in potassium with atenolol, presumably due to a $beta_2$-adrenoceptor blocking effect of atenolol upon membrane-bound sodium–potassium ATPase [11]. This may have contributed to the reduction in QTc lengthening during hypoglycaemia, observed following pretreatment with atenolol.

Atenolol is widely used in type 1 diabetic patients, and its safety profile is well established following work refuting theoretical concerns regarding hypoglycaemia unawareness and delayed recovery from hypoglycaemia [12]. Unlike unselective beta-blockers, which may prolong recovery from hypoglycaemia [12, 13], $beta_1$-selective agents such as atenolol do not inhibit hypoglycaemia-induced glycogenolysis, and although some hypoglycaemic symptoms (e.g. tremor) are reduced, others, such as sweating, are increased [12].

The widespread use of atenolol as a prophylactic measure to prevent sudden death from hypoglycaemia would clearly be inappropriate for such a rare condition. However, if we can develop ways of identifying those at particularly high risk the use of selective β_1-blocking agents could be a useful therapeutic option. We selected individuals who exhibited the greatest degree of QTc lengthening during previous experimental hypoglycaemia; the visit order was sequential (control followed by atenolol) rather than random. In one respect this was an important limitation of our study design, since it does not exclude the possibility that sympathoadrenal responses (and associated electrophysiological changes) are merely attenuated by repeated visits. However, in our previous study involving non-diabetic subjects, the randomised design clearly showed that reduced sympathoadrenal responses and QT lengthening were due to the effect of atenolol rather than repeated visits [4]. Furthermore, the present study design demonstrated the effectiveness of atenolol in attenuating QT lengthening in those who might be candidates for preventative therapy (i.e. those with the greatest QT increases during hypoglycaemia). However, such a strategy must wait until the link between QT lengthening and dangerous cardiac arrhythmias is more firmly established.

In summary, we have shown that atenolol blunts hypoglycaemic QTc lengthening in adults with type 1 diabetes. Whether such agents have a role in the prevention of sudden death associated with hypoglycaemia needs to be determined by additional research.

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