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Myocardial fibrosis and QTc are reduced following treatment with spironolactone or amiloride in stroke survivors: A randomised placebo-controlled cross-over trial ☆

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ABSTRACT

Introduction: Myocardial fibrosis is dysrhythmogenic and may contribute to the high incidence of cardiac death in stroke survivors, especially if they have long QTc. We tested the hypothesis that procollagen-1-carboxy terminal peptide (P1CP), a biomarker of myocardial fibrosis, might be improved following treatment with spironolactone or amiloride in stroke survivors. We also tested the hypothesis that both drugs would shorten QTc.
Methods: Study design: randomised, double-blinded, placebo-controlled, cross-over trial (spironolactone vs. amiloride vs. placebo).
Duration of Study: 3 months (1 month per drug).
Primary endpoints: P1CP, QTc
Results: 11 stroke survivors (5 female), aged 71 ± 4, BP 139/81 mmHg ± 20/11 mmHg, completed the study. Both spironolactone and amiloride significantly reduced P1CP [Spironolactone–Placebo = −24 ug/L, 95% CI = −40 to −6.9; Amiloride–Placebo = −28 ug/L, 95% CI = −44 to −11]. Spironolactone and amiloride both shortened QTc [Spironolactone vs. Placebo = −18 $ms^{1/2}$, 95% CI = −36 to −0.55; Amiloride vs Placebo = −25 $ms^{1/2}$, 95% CI = −42 to −7.5].
Conclusions: Procollagen-1-carboxy terminal peptide was reduced following treatment with spironolactone within a month. Further, this is the first study demonstrating amiloride could also improve myocardial fibrosis. The beneficial effects of both drugs on myocardial fibrosis, coupled with their effects on raising potassium translated to a shortening of QTc. Future studies should test the hypothesis that these drugs might reduce the risk of sudden cardiac death in stroke survivors.

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1. Introduction

Stroke is the third commonest cause of death in the UK. However, only part of the risk of death relates to the stroke itself. Indeed, if the patient survives the first 6 months after a stroke, the commonest cause of death in subsequent years is a cardiac death. During the time period of 1–2 years after a stroke, cardiac deaths would account for 56% of all deaths whilst recurrent strokes would only account for 15% [1]. Long QTc predicted future cardiac deaths in stroke survivors [2]. We then performed a prospective study which showed that QTc was more prolonged in stroke survivors with left ventricular hypertrophy (LVH) [3]. LVH is characterised histologically by myocyte hypertrophy and myocardial fibrosis, which is dysrhythmogenic.

Diuretic-induced potassium and magnesium deficiency could also contribute to QT prolongation, cardiac arrhythmias and sudden death [4]. This mechanism could be relevant in explaining the 30% survival advantage seen with spironolactone in the RALES trial [5] since spironolactone increases plasma potassium and shortens the QT interval. However, other mechanisms are also likely to contribute to spironolactone's beneficial effect on mortality in RALES. These are spironolactone's ability to improve endothelial dysfunction, heart rate variability and procollagen III N-terminal peptide (PIIINP)—a marker of myocardial fibrosis. In previous work in heart failure, we found that amiloride also increased plasma potassium and shortened the QT interval but had no effect on endothelial dysfunction, heart rate variability and collagen markers [6]. Presumably the effects of spironolactone and amiloride on the QT interval were due to potassium retention per se whilst spironolactone's effects on endothelial function, heart rate variability and myocardial fibrosis were due to aldosterone blockade which amiloride does not do. Nevertheless, to our knowledge, this has not been studied in patients who do not have heart failure.

The prospect arises that increasing serum potassium even within the normal range may have a beneficial effect on long QT intervals,

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irrespective of the reasons underlying the long QT interval in the first place. We therefore tested the hypotheses that spironolactone and amiloride would both raise blood potassium and shorten the QT interval in stroke survivors who had prolonged QT intervals. We also took this opportunity to see if spironolactone or amiloride would reduce P1CP, a plasma marker of myocardial fibrosis.

2. Patients and methods

The study cohort included twelve stroke survivors who had a relatively long QT interval despite already being on an ACE-inhibitor or angiotensin-II-receptor antagonist (unless if the drugs were contra-indicated or not tolerated). The latter drugs were included in order to match the HOPE and PROGRESS studies [7,8] where ACE-inhibitors had been shown to benefit stroke survivors.

The study design was a randomised, double-blinded, placebo-controlled, cross-over trial (between spironolactone 25 mg od, increased to 50 mg od after 1 week if tolerated; amiloride 5 mg od, increased to 10 mg od if tolerated, and placebo). All the capsules were matched in appearance. No wash-out period was required between different treatments because the treatment periods were relatively long (1 month). After oral administration, spironolactone is largely converted in the gut and liver to the active metabolite canrenone, which has a plasma half-life of 9 h only. Similarly, the maximum effect of amiloride occurs about 6 h after an oral dose and the action may last 24 h only.

Ethical approval has been obtained from the Tayside Committee on Medical Research Ethics. All patients gave their informed consent to the study.

The patients attended hospital to have their pulse rate and blood pressure checked, an ECG and have their blood potassium and other blood tests (sodium, urea, creatinine) very carefully monitored for 1 week after commencement of each new drug, 1 week after the dose change, and after 1 month of treatment, just prior to switching to one of the other drugs. In addition other blood tests (magnesium, calcium, BNP, P1CP) and echocardiography were performed along with assessment of symptoms at baseline and at the end of the 1 month of treatment with each of the drugs. The medication was stopped instantly if in any patient the plasma potassium was elevated above 5.4 mmol/L. If there were intolerable side-effects, the dose was reduced to 1 capsule /day or even 1 capsule every 2–4 days.

The ECGs were analysed by a single observer (SW) who was not only blind to the treatment the patient is on, but also to the outcome of the blood tests, echocardiogram and clinical findings.

QTc was measured from lead III.

2.1. Blood tests

The blood was aliquoted into appropriate tubes stored on ice, with all samples bar P1CP being spun immediately at 3000 rpm for 10 min at 5 °C in a Biofuge 28 RS centrifuge, Heraeus Instruments, UK. The P1CP samples were left for at least 20 min at room temperature, to allow the clot to retract, prior to spinning as above. All sample bar BNPs were stored at −20 °C immediately after aliqouting into fresh tubes. The BNP samples were stored at −70 °C. Reliability information was obtained using the coefficient of variation data from our laboratory in Dundee.

2.2. P1CP

The concentration of P1CP was measured by radioimmunoassay using a kit from Orion Diagnostics, Finland (assay coefficient of variation; = 1.48%).

2.3. Potassium

Serum Potassium levels were measured by indirect ion selective electrode on a Roche/Hitachi 917 analyser, which was manufactured in Japan. Quality control was run at 2 levels: coefficient of variation = 1.8% for mean 2.85 mmol/L, 1.0% for mean 5.97 mmol/L.

2.4. Magnesium

Magnesium levels were measured by colorimetric determination on a Cobas Bio, Roche, UK, using a kit from Sigma Diagnostics, UK (coefficient of variation; inter = 2.48%, intra = 1.12%).

2.5. Corrected calcium

Corrected calcium was calculated as Total Ca^{2+} (mmol/L) + [0.018 × (46.5 − albumin g/L)]. Calcium levels were measured by colorimetric determination on a Cobas Bio, Roche, UK, using a kit from Sigma Diagnostics, UK (CV, inter = 1.35%, intra = 1.24%).

Albumin levels were measured by colorimetric determination on a Cobas Bio, Roche, UK, using a kit from Sigma Diagnostics, UK (coefficient of variation; inter = 2.97%, intra = 4.31%).

2.6. Brain natriuretic peptide (BNP)

BNP was extracted from plasma using C_{18} columns and then measured by radioimmunoassay, Bachem, UK (coefficient of variation; inter = 15.5%, intra = 12.2%).

Echocardiography was performed to assess left ventricular mass index. Transthoracic echocardiography was done using the Hewlett Packard SONOS Phased Array Imaging System (HP 2000).

2.7. Left ventricular mass index estimations

Intraventricular septal thickness in end-diastole (IVSd), end-diastolic left ventricular internal dimension (LVIDd) and left ventricular posterior wall thickness in end-diastole (PWTd) were measured from M-mode measurements, obtained at the level of the papillary muscles from parasternal views [9]. When the echocardiogram was of sufficient research quality, left ventricular mass index (LVMI) was calculated using the American Society of Echocardiography guidelines and measurements were made from “leading edge to leading edge”.

$$\mathrm{LVMI} = \left\{0.83 \times \left[(\mathrm{LVIDd} + \mathrm{PWTd} + \mathrm{IVSd})^3 - (\mathrm{LVIDd})^3\right] - 0.6g\right\}/\mathrm{BSA}$$

$$\mathrm{BSA}\left(\mathrm{m}^2\right) = \text{Body Surface Area}$$
$$\left(\text{defined as } 0.0001 \times 71.84 \times \mathrm{Weight(kg)}^{0.425} \times \mathrm{Height(cm)}^{0.725}\right)$$

2.8. QT measurements

The resting ECGs were analysed by a single observer (SW) who was not only blind to the treatment the patient was on, but also to the outcome of the blood tests, and clinical findings.

The start of the Q wave and the end of the T wave were located in lead III on the 12-lead ECG. The T wave end was defined as the point when the T wave returned to the isoelectric line. If this point was not clearly defined, then the reading would be omitted. If the T wave was followed by a U wave, then the nadir between the T and the U wave (i.e. the lowest point of the curve) would be taken as the point where the T wave ended. These readings were entered into the digitising programme, which calculated mean QT from up to 3 readings. To work out the heart rate corrected QT interval (QTc), R–R intervals were similarly

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