Withdrawal of long term diuretic medication in elderly patients: a double blind randomised trial

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Abstract

Objectives: About 20% of elderly people use long term diuretic medication, but there is doubt whether prolonged diuretic medication on such a large scale is necessary. We performed a study to assess what proportion may successfully be withdrawn from diuretic therapy.

Design: Double blind randomised controlled trial with six month follow up.

Setting: General practice.

Subjects: 202 patients taking long term diuretics without manifest heart failure or hypertension.

Interventions: Patients were allocated to either placebo (withdrawal group, n = 102) or continuation of diuretic treatment (control group, n = 100).

Main outcome measure: Occurrence of clinical conditions requiring diuretic therapy based on fixed criteria.

Results: During follow up diuretic therapy was required in 50 patients in the withdrawal group and 13 in the control group (risk difference 36%; 95% confidence interval 22% to 50%). Heart failure was the most frequent cause of prescribing diuretic therapy (n = 25). Cessation of diuretic therapy caused a mean increase in systolic blood pressure of 13.5 (9.2 to 17.8) mm Hg and in diastolic pressure of 4.6 (1.9 to 7.3) mm Hg.

Conclusion: Withdrawal of long term diuretic treatment in elderly patients leads to symptoms of heart failure or increase in blood pressure to hypertensive values in most cases. Any attempt to withdraw diuretic therapy requires careful monitoring conditions, notably during the initial four weeks.

Introduction

Diuretics are among the most frequently prescribed drugs in Western societies, with about 20% of elderly patients using them long term.[1-3] Heart failure and hypertension are the major indications, and the cost effectiveness of diuretics in these conditions is well established. Inappropriate prescribing, however, based on premature indications or uncritical repetitions of prescriptions, leads to unnecessary use of diuretics and should be minimised because of potentially serious side effects such as hypokalemia, hyponatriemia, dehydration, and cardiac arrest.[4-6] For the treatment of hypertension, dose reduction or cessation is generally recommended when blood pressures remain within normal limits over one to two years of treatment.[7 8] In heart failure new insights about the harmful long term effects of chronic activation of the renin-angiotensin-aldosterone system by diuretic therapy have led to an increasing number of recommendations to aim for the lowest possible dose of diuretics.[9-11] The possibility of withdrawing diuretic therapy in patients with heart failure but no signs of congestion has been studied in only one randomised trial, which replaced diuretics with angiotensin converting enzyme inhibitors.[12]

Primary care physicians account for most diuretic prescriptions.[1] We therefore performed a double blind randomised trial among elderly patients in general practice to assess what proportion could be successfully withdrawn from diuretic therapy.

Methods

Protocol

Patients aged 65 or more who had been receiving diuretics for at least six months and had no overt heart failure or hypertension were eligible for the trial. By scanning the pharmacy registers of eight general practices we identified 470 patients receiving long term diuretic therapy, of whom 268 were excluded because of a history of acute heart failure, defined as admission to hospital or prescription of intravenous diuretic therapy (27); symptoms of heart failure during the previous three months (21); manifest heart failure, defined as a heart failure score (see below) of over 4 (39); use of frusemide at dosages over 80 mg/day (26); mean of three blood pressure values (two measured at successive home visits and one obtained from the medical file) $>180/100$ mm Hg (21); hypercalciuria, nephrotic syndrome, and glaucoma (2); use of fixed combinations of diuretics with β blockers or angiotensin converting enzyme inhibitors (25); combination therapy of β blockers, diuretics, and vasodilators for hypertension (2); use of a diuretic for which no placebo was available (40); and non-compliance during the run in phase (1). In addition, 57 patients or their general practitioners refused to cooperate and seven eligible patients could not be enrolled in the trial for logistic reasons.

Each general practitioner filled out a questionnaire to assess the patient's current indications for diuretic treatment. The sample size calculation was based on the assumption that a difference of 20% between the

interventions was clinically relevant and a formula was used as given by Pocock.[13] The protocol was approved by the medical ethics committee of Erasmus University/Academic Hospital Dijkzigt Rotterdam and written informed consent was obtained from all patients.

Outcomes

The primary outcome variable was successful withdrawal from diuretic therapy. Patients in the withdrawal group who were still taking blinded study medication at the end of the six month follow up period were considered successfully withdrawn. Those patients who met one of the predefined criteria for requiring diuretic therapy within the follow up period were considered to be unsuccessfully withdrawn. Criteria for prescription of diuretic therapy were: (*a*) heart failure score exceeding 4 points or (*b*) a mean of three duplicate systolic or diastolic blood pressure measurements on separate occasions of >180 mm Hg or >100 mm Hg, respectively. Further, patients in whom diuretic therapy was restarted by their doctor for other reasons—for example, symptoms of increased shortness of breath—were considered to be unsuccessfully withdrawn. Changes in systolic and diastolic blood pressures are presented as secondary outcomes.

Baseline assessments and assignment

The run in phase of four weeks included two home visits (by EPW and CvD) to collect baseline data and perform the randomisation. At the first visit all diuretic medication was handed over to the research physician and replaced by active run in medication of the corresponding diuretic. At the second home visit, at the end of the run in phase, each patient was randomly assigned to placebo (the withdrawal group) or continuation of diuretic therapy (the control group), after stratification by age (65-79 and >80 years) and type of diuretic. Blocks of four sets of study medication each consisted of two placebo and two genuine packages, which were consecutively assigned to enrolled patients. Patients with frusemide dosages of 40 or 80 mg/day went through a dose halving regimen of one and two weeks, respectively, to prevent severe rebound effects. Dose halving was started immediately after randomisation and was performed double blind. Randomisation lists and numbered sets of study medication were generated by the trial pharmacist of the Academic Hospital, who also produced sealed envelopes with decoding information for emergencies.

Blinding procedure and drug compliance

Matching placebo was available for the five diuretics or fixed diuretic combinations most often prescribed in our region: frusemide, chlorothalidone, hydrochlorothiazide plus triamterene, epitizide plus triamterene, and triamterene, covering 90% of all diuretic use. The similarity of genuine and placebo tablets ensured the impossibility of recognising them by colour, form, or taste. The randomisation list remained in the pharmacy of the Academic Hospital in Rotterdam, separate from the trial centre in Schoonhoven. Of the sealed envelopes one copy was kept in the trial centre and another with the patient at home (for emergencies). The codes were broken either after the assessment of the last set of data, or when a diuretic prescription was needed, in which case the primary outcome of the study became actual. This blinding procedure was tested one month after randomisation by asking both the patient and the trial doctors their opinion about the content of the trial medication. Drug compliance was checked by counting tablets and asking patients about compliance at every follow up contact and by assessment of serum diuretic concentrations (with high pressure liquid chromatography and ultraviolet fluorescence for chlorothalidone, triamterene, and frusemide) at the start and the end of the study.

Follow up

During follow up participants were visited six times at their homes by study physicians (EPW, CvD)—2 days, 1 and 2 weeks, and 1, 3, and 6 months after randomisation. Heart failure score and blood pressure were assessed at baseline and at all follow up visits. Heart failure symptoms were measured by means of a scoring list, including paroxysmal nocturnal dyspnoea in the preceding week (3 points); dyspnoea on exertion in the preceding week (2 points); raised jugular venous pressure (2 points); heart rate >100 beats/min (1 point); hepatojugular reflux (1 point); lower pulmonary crepitations (1 point); S3 gallop rhythm (1 point); two sided pitting ankle oedema (1 point); and hepatomegaly (1 point). This symptom score list was validated separately.[14]

During the study duplicate blood pressure readings were taken with an Omron HEM-403C oscillometric automatic device with the patient sitting.[15] The arm with the highest blood pressure was determined at the first session and used throughout for further measurements. An electrocardiogram was recorded at baseline.

Data analysis

The frequency of fulfilling one of the criteria for prescription of diuretic treatment in the withdrawal and the control group was compared by calculating risk differences with 95% confidence intervals and, in case of survival analysis, by log rank tests. Effects on blood pressure were assessed by calculating differences (with 95% confidence intervals) between the mean changes in these variables in the withdrawal and the control group. Mean changes in variables were calculated by subtracting the baseline value from the last available value after randomisation. Analyses were carried out by the intention to treat principle. Patients who fulfilled one of the criteria for prescription of diuretic treatment during the trial had their last double blind measurement of the secondary outcome variables carried forward to subsequent time points (carry forward principle). We decided in advance to perform subgroup analyses according to age (65-79 and >80 years), sex, and indication for diuretic therapy (heart failure, hypertension, and non-cardiac ankle oedema). Interaction tests were applied to compare subgroups.[13]

Results

Figure 1 summarises the participant flow and the trial design. Of 202 patients included (53 men and 149 women) the indications for diuretic therapy at the time

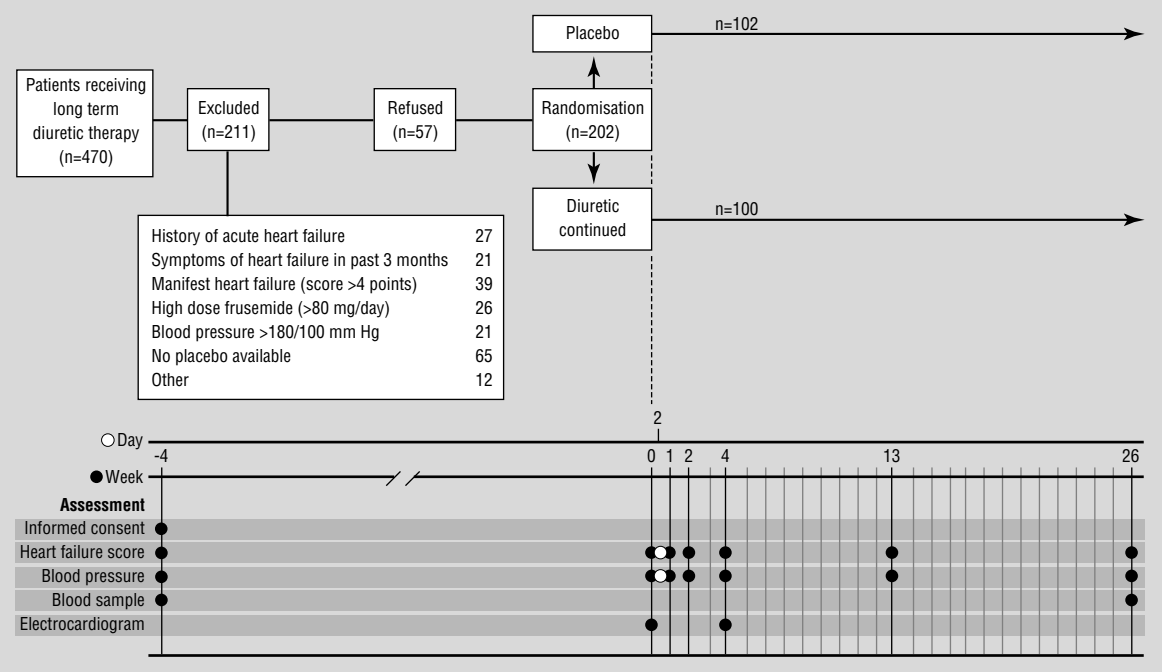

Fig 1 Study design and number of patients recruited

of entry into the trial were heart failure (42%), hypertension (43%), and non-cardiac ankle oedema (14%). Frusemide was used by 32% of the patients, thiazides (alone or in combination with triamterene) by 66%, and triamterene alone in 2%. Of 202 patients, 102 were randomly assigned to the withdrawal group and 100 to the control group. The two groups were similar in all relevant baseline characteristics (table 1).

Table 1 Baseline characteristics of the participants. Values are means (SE) or numbers of patients

Characteristic	Withdrawal group (n=102)	Control group (n=100)
Age (years)	76 (1)	76 (1)
Women	81	70
Current indication for diuretic therapy:		
Heart failure	46	38
Hypertension	42	46
Oedema	13	15
Other/unknown	1	1
Heart failure score (0-13)	1.4 (0.1)	1.5 (0.1)
New York Heart Association classification of all patients:		
1 (no limitation of physical activity)	82	77
2 (some limitation)	16	19
3 (marked limitation)	3	4
4 (severe limitation)	1	0
Systolic blood pressure (mm Hg)	147 (2)	147 (2)
Diastolic blood pressure (mm Hg)	81 (1)	81 (1)
Irregular pulse	26	28
Previous myocardial infarction:		
Clinical diagnosis	11	14
Electrocardiographic diagnosis	14	15
Diuretic therapy:		
Frusemide (including combinations with other diuretics)	31	33
Thiazide (including combinations with triamterene)	66	65
Triamterene monotherapy	5	2
Diuretic dose:		
<1 Defined daily dose	27	35
=1 Defined daily dose	68	55
>1 Defined daily dose	7	10
Duration of diuretic therapy (years)	7.2 (0.5)	7.6 (0.6)

Success of withdrawal

During the six month follow up 50 patients in the withdrawal group and 13 in the control group fulfilled the criteria for prescription of diuretic therapy (risk difference 36%; 95% confidence interval 22% to 50%). Development of symptoms of heart failure was the most frequent reason: 25 patients in the withdrawal group and 4 in the control group (table 2). The probability of requiring diuretic therapy in the two groups was highest in the first four weeks after randomisation (fig 2). During the study period none of the patients died or had to be admitted to hospital.

Effect on blood pressure

The difference in mean systolic and diastolic blood pressures between the withdrawal group and the control group gradually increased after withdrawal of diuretics by, respectively, 13.5 (95% confidence interval 9.2 to 17.8) mm Hg and 4.6 (1.9 to 7.3) mm Hg (fig 3).

Subgroup analyses

Patients who used diuretics because of heart failure fulfilled the criteria for prescription of diuretic therapy more often than those taking them for hypertension or non-cardiac ankle oedema. Percentages of patients with these indications in the withdrawal group who needed prescription of diuretic therapy were 65%, 38%, and 23% respectively. The corresponding risk differences were 57% (36% to 78%), 21% (2% to 40%), and 10% (−11% to 31%). Women more often needed additional diuretic therapy (risk difference 40% (25% to 55%)) than men (26% (1% to 51%)). The increase in blood pressure was more prominent in women (16.3/5.9 mm Hg) than in men (5.3/−1.3 mm Hg) (interaction tests P = 0.03/P = 0.04). No marked differ-

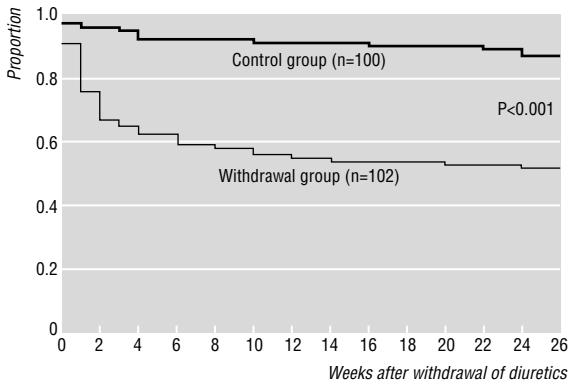

Fig 2 Kaplan-Meier analysis of cumulative probability of successful withdrawal of elderly patients from diuretic therapy

ences were found in subgroup analyses according to age.

Blinding procedure and drug compliance

The patients correctly guessed whether they were allocated to the withdrawal or the control group in 62% of cases, while their doctors guessed correctly in 65%. The data analysist (EPW) was blinded until the allocation codes had been entered in the SPSS spreadsheet. On the basis of serum concentrations of diuretics at baseline and at completion, tablet counting, and questions about compliance at each visit, we estimated drug compliance during the trial to be at least 90% in both groups.

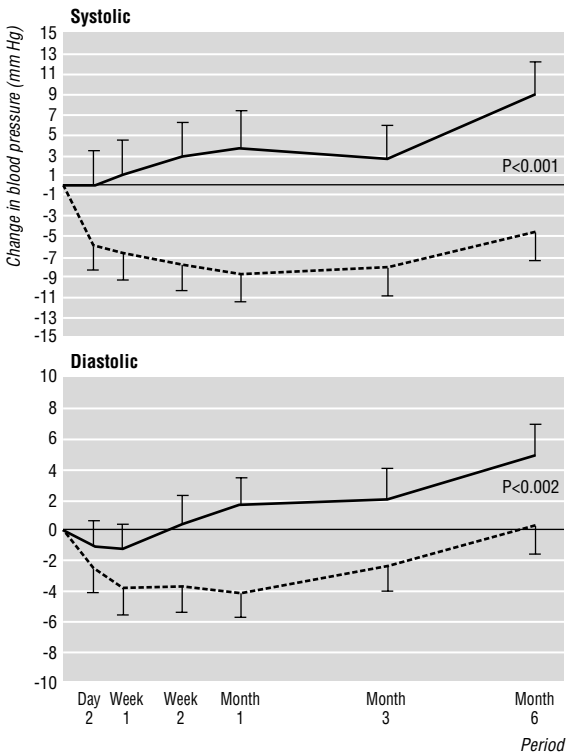

Fig 3 Effect of withdrawal of diuretic therapy in withdrawal group (solid line) and control group (dotted line) on systolic and diastolic blood pressure. Bars represent 95% confidence intervals. Patients who required diuretic therapy during the follow up period had their last double blind measurement carried forward to subsequent time points

Table 2 Patients meeting one of the predefined clinical criteria requiring reinitiation of duiretic therapy. Results are numbers of patients

Criterion	Withdrawal group (n=102)	Control group (n=100)	Risk difference (%) (95% CI)
All	50	13	36 (22 to 50)
Heart failure*	25	4	21 (11 to 31)
Hypertension*	9	5	4 (–3 to 11)
Subjective shortness of breath	6	0	6 (1 to 11)
Non-cardiac ankle oedema	4	1	3 (–1 to 8)
Miscellaneous clinical conditions	3	1	2 (–2 to 6)
Other	3	2	1 (–3 to 5)

* The reason for reinitiation was classified as heart failure if patients had heart failure scores >4 points and as hypertension if the mean value of three consecutive systolic or diastolic blood pressure measurements on different occasions was >180 mm Hg or >100 mm Hg respectively

Discussion

Our findings indicate that withdrawal of long term diuretic therapy in elderly patients without manifest heart failure or hypertension is often accompanied by the occurrence of symptoms of heart failure or a rise in blood pressure. Despite the preselection of 202 patients out of 470 long term diuretic users, the predefined criteria for prescribing diuretic treatment were fulfilled in 49% of patients withdrawn from diuretics and in 13% of those continuing diuretic therapy (risk difference 36% (95% confidence interval 22% to 50%). The risk difference was most pronounced in those prescribed diuretics for heart failure.

The vast majority of clinical conditions requiring reinitiation of diuretic therapy occurred during the first four weeks after withdrawal. This indicates that rebound cannot be ruled out and a more prudent weaning off procedure might have produced a higher rate of successful withdrawal.

Withdrawal led to a considerable increase in blood pressure, though a marked decrease in blood pressure in the control group constituted a substantial part of this blood pressure effect. This phenomenon may be explained by a progressive decrease of stress in patients during the blood pressure measurements at serial follow up visits. In this population of patients with a mean age of 76 years and mean baseline blood pressure of 147/81 mm Hg the observed increase in blood pressure may generally be considered an unwanted effect, leading to an increased risk of cardiovascular disease, though in some patients it may reflect a beneficial correction of relative dehydration.

The effect of withdrawing diuretics on blood pressure and on the probability of developing symptoms of heart failure was considerably more pronounced in women than men. Because only marginal sex differences in the effect of thiazides on blood pressure and on diuresis are reported in the literature, no clear explanation for this finding exists, and its reproduction in another study should be awaited before more definite conclusions can be drawn.[16]

This study included patients who took diuretics for heart failure, hypertension, or non-cardiac ankle oedema. The reason for studying such a heterogenous group was implicit to our research objective: to assess the proportion of all elderly patients taking diuretics who could successfully be withdrawn from diuretic therapy. Subgroup analyses showed that after withdrawal of diuretic therapy symptomatic heart failure developed most often among patients prescribed

diuretics for heart failure, but an increase in the symptoms of heart failure also often occurred in patients with other indications. Hypertension is a major risk factor for heart failure and possibly many of the patients taking diuretics for hypertension had gradually developed latent heart failure, while some patients who took diuretics for non-cardiac ankle oedema may have been suffering from (asymptomatic) heart failure.

Many earlier studies on withdrawal of diuretics did not include a comparison group, and of the controlled trials only a minority included placebo treatment.[17 18] The need for a control group to take into account the natural history of the conditions studied and extraneous factors is illustrated by our results: although 49% of the patients in the withdrawal group needed to have diuretic therapy prescribed, as many as 13% of the control group—who continued to receive diuretics—also needed to have it prescribed. Furthermore, differences in blood pressure were largely caused by a decrease in the control group and would have been missed in an uncontrolled trial.

The proportion of patients from whom diuretics could successfully be withdrawn in our study was not as large as in previous studies. Two earlier controlled randomised trials of withdrawal studied 106 patients in geriatric hospital wards and 77 patients in geriatric institutions, with follow ups of three and 12 months respectively.[17 18] The proportions of patients withdrawn from treatment were 76% and 71% compared with 49% in our study. The risk differences of "clinical need for reinitiating diuretic therapy" between the placebo and the control group in these studies were only 16% (2% to 30%) and 8% (−12% to 28%), while we found a larger difference of 36% (22% to 50%). The difference between these two trials and ours is in the selection of institutionalised patients in the former studies. Apparently unnecessary prescribing is more prevalent in these populations.

Though the effectiveness of diuretics in heart failure and hypertension is well established, potential adverse effects of diuretics in elderly patients justify regular evaluation of the possibility of stopping diuretics. Redundant medication represents an important quality of care problem in elderly patients.[19] However, about 50% of all patients withdrawn from long term diuretic therapy in our study required reinitiation of diuretics within six months. Even among those not fulfilling one of the reinitiation criteria, withdrawal often provoked some mild symptoms of heart failure or an unfavourable increase in blood pressure. We conclude that stopping diuretics in elderly patients does more harm than good in most cases, particularly those with heart failure. Attempts to withdraw diuretic therapy require extensive monitoring, especially during the first four weeks, and should be restricted to patients with hypertension and non-cardiac oedema.

Key messages

- Many elderly people receive long term diuretic therapy, 45% for hypertension, 40% for heart failure, and 15 % for non-cardiac ankle oedema
- After withdrawal of diuretics in a preselected group of elderly patients (with no manifest heart failure and satisfactorily regulated blood pressure) about half needed to restart diuretics during the next six months, usually because of heart failure
- Average blood pressures rose considerably, by 13.5/4.6 mm Hg
- Withdrawal of diuretic therapy does more harm than good in most patients, notably in those with heart failure
- Rigid monitoring is needed in any attempt to withdraw diuretic therapy

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