Short term effect of withdrawal of diuretic drugs prescribed for ankle oedema

J W de Jonge, J A Knottnerus, W M van Zutphen, G A de Bruijne, H A J Struijker Boudier

Abstract

***Objective*—To determine the effect of withdrawing diuretic drugs on oedema in patients prescribed them for only ankle oedema, excluding patients with cardiac, hepatic, or renal failure.**

***Design*—Randomised controlled trial.**

***Setting*—15 general practices in the Netherlands.**

***Patients*—1202 patients aged 65 years or older and taking diuretic drugs, 63 of whom were eligible for the trial.**

***Main outcome measure*—Change in volumetrically determined ankle oedema (oedema index) over six weeks.**

***Results*—34 patients were randomised to stop diuretics and 29 to the control group. In eight patients diuretics had to be restarted. Among patients who had diuretics withdrawn successfully, rebound oedema caused a temporary increase in mean oedema index. The peak level (3·5% (95% confidence interval 1·5% to 5·2%) was reached in the third week, after which the oedema seemed to be returning to the baseline level.**

***Conclusion*—Few patients who have been prescribed diuretics for only ankle oedema clearly have no contraindications to withdrawing diuretics. If patients are unlikely to have cardiac insufficiency and careful monitoring is provided, withdrawal of diuretics seems to be feasible, though moderate rebound oedema may occur for a short time.**

General practice

- Concern has been raised about the unnecessary use of diuretics by elderly patients
- Withdrawal can be appropriate in elderly patients taking diuretics for ankle oedema provided that the oedema is not caused by cardiac, renal, or hepatic insufficiency
- In this study 17% of the patients taking diuretics for ankle oedema were eligible for withdrawal
- Withdrawal was successful in 26 of 34 patients
- Patients should be closely monitored after withdrawal as they may develop a temporary increase of ankle oedema

Introduction

General practitioners often have to decide whether to stop or continue long term treatment with drugs. Although much is known about the effects of starting drugs, little is known about the effects of their withdrawal. In this context, diuretic drugs prescribed for ankle oedema are of interest. It has been suggested that ankle oedema is a misleading sign, only occasionally being associated with heart failure.[1,2] Withdrawal of diuretics has been suggested for elderly patients with ankle oedema provided that the oedema is not caused by cardiac, renal, or hepatic insufficiency.[3-6] However, no evidence exists from randomised trials on the effects of withdrawal of diuretics prescribed for ankle oedema. We conducted a randomised controlled trial of the course of ankle oedema after withdrawal of diuretics in elderly patients.

Patients and methods

We identified patients aged 65 and over taking diuretic drugs in 15 practices from medical and pharmacy files and used a questionnaire to select those taking the drugs for ankle oedema. Eligibility for the trial was established on the basis of a clinical examination since patients prescribed diuretics for heart failure could have reported taking them for ankle oedema. We tried, however, to include patients who had had heart failure diagnosed on insufficient grounds.[1,2] We excluded patients who took less than one dose of diuretics a week; had oedema caused by the nephrotic syndrome or liver cirrhosis; took diuretics for hypertension; had a terminal illness; were in hospital; had decreased mental functioning; had crural ulcer; or had congestive heart failure or increased risk of developing it after stopping diuretic drugs. Criteria for the risk of developing congestive heart failure after stopping treatment were derived from Carlson *et al.*[7] Patients were also excluded if they had had heart failure previously established by a cardiologist, history of severe dyspnoea treated by the general practitioner as cardiac failure, atrial fibrillation, symptoms of right sided heart failure, palpable right ventricular pulsations, or hepatomegaly. After giving their written consent, eligible patients were randomly assigned to an intervention group (stopping diuretic drugs) or a control group (containing diuretic drugs). Randomisation was prestratified in each practice. Patients were monitored for six weeks.

Oedema was measured at baseline (t_0) on the second or third day of the first week (t_1), on the fourth or the fifth day of the first week (t_2), and thereafter once weekly for six weeks (t_3 to t_7) by determining the volume of the foot and ankle by water displacement.[8] The relative changes in local oedema at the respective follow up times were expressed as $((Vol(t_i)-Vol(t_0))/Vol(t_0)) \times 100 =$ oedema index (%), where $Vol(t_i) =$ volume of left foot and ankle plus right foot and ankle at t_i and $Vol(t_0) =$ volume of left foot and ankle plus right foot and ankle at t_0. To monitor compliance we obtained urine samples at t_0, t_2, and t_7 and analysed them for diuretic drugs.

We calculated that to detect a difference in mean oedema index of at least 5%, given an estimated standard deviation of 5% and $\alpha = \beta = 0{\cdot}05$, required at

University of Limburg, PO Box 616, 6200 MD Maastricht, Netherlands
J W de Jonge, *assistant researcher, department of general practice*
J A Knottnerus, *professor*
W M van Zutphen, *associate professor*
G A de Bruijne, *assistant professor*

Department of Pharmacology, University of Limburg, Netherlands
H A J Struijker Boudier, *professor*

W M van Zutphen has died since this paper was completed.

Correspondence to:
Dr de Jonge.

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least 26 patients per group.[9] We used the BMDP-90 statistical program for analysis.[10] The χ^2 test or, when appropriate, Fisher's exact test was used to compare proportions (two sided significance level $P < 0.05$). We used the BMDP 5V repeated measures analysis program to check the shape of the follow up curve, taking into account the following potential codeterminants: type of diuretic drug (loop diuretics (frusemide or bumetanide) versus all other diuretics); dose of diuretics (one daily dose versus less than one daily dose); mobility of the patient (not mobile (defined as a sedentary daily life) versus mobile); time of day of the observation; maximum day temperature; symptoms of chronic venous insufficiency (at least one symptom except oedema versus no symptoms); pitting oedema at baseline (present or absent); concomitant use of digoxin, β blocking drugs, or vasodilating drugs. The follow up times were represented both as linear and quadratic terms and in interaction with withdrawal.

Results

A total of 1202 patients met the age and prescription criteria; 383 patients stated that they they took diuretics for ankle oedema. From this group we excluded 202 because of increased risk of developing congestive heart failure after withdrawal, 69 for hypertension as concomitant indication, and 30 because they did not meet other selection criteria. Nineteen patients refused to participate. Thus 63 patients were enrolled in the trial (34 in the intervention group, 29 in the control group). Thirty four patients were aged 65 to 74 years of age, 23 patients 75 to 84 years, and six patients 85 years or older. There were 55 woman and eight men. We found no differences between the two groups with regard to age, sex, use of loop diuretics, dose taken, oedema, chronic venous insufficiency, dietary salt, mobility, use of compression therapy, and concomitant use of digoxin, β blocking drugs, and vasodilating drugs. Table I shows the diuretic drugs taken.

Diuretic drugs were restarted in eight patients. Three patients developed symptoms suggesting heart failure: two of them showed increase of weight and oedema, and complained of fatigue and dyspnoea, and a woman of 88 years developed strong oedema. After diuretics were restarted the symptoms quickly returned to the baseline level. Another patient developed systolic high blood pressure. Two patients did not like the measurement procedures and were worried about the withdrawal of diuretics. One patient felt unwell and experienced incontinence of urine. Finally, one patient dropped out because of an unexpected holiday.

TABLE I—*Diuretics taken before start of the trial*

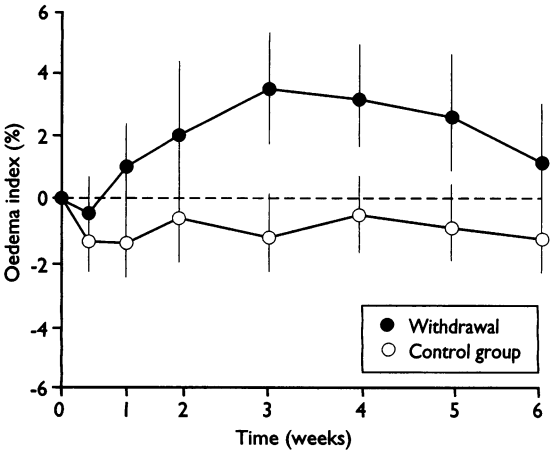
	No in intervention group	No in control group
Frusemide	9	9
Frusemide plus triamterene	1	3
Frusemide plus amiloride	0	1
Frusemide plus hydrochlorthiazide-amiloride*	1	0
Hydrochlorthiazide-amiloride*	6	7
Hydrochlorthiazide-triamterene*	5	4
Triamterene	3	0
Epitizide-triamterene*	3	1
Bumetanide	2	1
Amiloride	1	1
Hydrochlorthiazide	2	0
Chlorthalidone	0	1
Mefruside	0	1
Spironolactone plus hydrochlortriazide-triamterene	1	0
Total	34	29

*Combined preparation.

TABLE II—*Analysis for time effect. Estimated coefficient for independent variables in model predicting oedema index curves for intervention group and control group*

Parameter	Estimated coefficient	Z score	P value
Constant	0·010	1·77	0·08
Withdrawal*	0·017	3·05	<0·01
Time (linear)	0·002	1·62	0·11
Time (quadratic)	−0·002	−5·07	<0·01
Withdrawal* time (linear)	0·001	1·40	0·16
Withdrawal* time (quadratic)	−0·002	−3·72	<0·01

The banded covariance structure was chosen. Each fixed effect of the model decomposed into single degree of freedom regression terms and covariates is represented in the table.
*Withdrawal (1=yes, 0=no).



Oedema index (mean and 95% confidence intervals) during the six week follow up

Further analysis was restricted to the 55 patients who completed the trial. Overall compliance according to the urine samples was 89% at the end of the first week and 88% at the end of the trial. The compliance in the intervention group was over 92% at both these times. The mean oedema index in the intervention group peaked in the third week at 3·5% (95% confidence interval 1·8% to 5·2%). This is a significant rise compared with the control group (figure).

In repeated measures analysis none of the studied codeterminants significantly affected the oedema index. Withdrawal of loop diuretics compared with other diuretics increased the oedema index by 1·2% and the difference was not significant. Analysis in the reduced model, limited to the independent variable withdrawal or continuation of diuretics, showed no significant difference in linear effect of the observation time between both groups. However, a quadratic effect of the observation time clearly appeared (table II). This strongly indicates that the curves for both groups in the figure are appropriate.

Discussion

Since only 17% of the patients taking diuretics for ankle oedema seemed to be eligible for withdrawal, the problem of misuse of diuretics for ankle oedema may not be as widespread as has been suggested.[1] Many patients had contraindications for the withdrawal of diuretic treatment though these were sometimes based on uncertainty about the indications. The strength of the indication for prescribing diuretics should be considered carefully before starting treatment since, once started, diuretics are not easily withdrawn.

Eight of the 34 patients in the withdrawal group required diuretics to be restarted. In four cases not resuming diuretics might have led to serious consequences. However, in practice patients who develop fluid retention with possible complications could be identified in time by making frequent follow up visits and giving clear instructions to patients about when to enlist medical help.

Diuretic induced oedema was described more than 15 years ago as a rebound effect after withdrawal of diuretics and lasts up to three weeks in most patients.

It was suggested that this was the result of rebound stimulation of the renin-angiotensin-aldosterone system.[11 12] We also found that withdrawal of diuretic drugs leads to an initial increase in oedema. The process seems to be reversible in patients in good health. Six weeks after diuretic therapy was stopped the oedema, although still decreasing, had almost reached the starting level.

We chose to study the effects of withdrawal by comparing a group in which withdrawal was open with a group in which treatment was continued. We therefore cannot separate the pharmacological effect and the placebo effect. However, it is not likely that a psychological effect would have had an important influence on our outcome measure. Moreover, for general practitioners it is more relevant to know the total effect of stopping drugs openly.

We found no significant differences in effects between various types of diuretics. The power of the trial may not have been sufficient to detect such an effect and more extensive investigations with a longer follow up and larger study population would be useful. We conclude that if cardiac insufficiency is unlikely and careful monitoring is provided, withdrawal of diuretics is feasible in elderly patients who have been prescribed diuretics for ankle oedema. After withdrawal patients may develop moderate oedema, which in most cases seems to be temporary.

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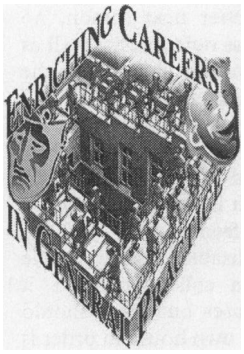
Enriching Careers in General Practice

New roles for general practitioners

Stuart Handysides



This is the last in a series of articles examining ways to increase fulfilment from a career in general practice.

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Stuart Handysides, *editorial registrar*

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General practice is likely to change greatly over the next few years. Increases in care in the community and day surgery will lead to more work, and the demand for better data on practice activity will mean the development of audit and epidemiological work. To make time general practitioners will have to learn to delegate work that does not require a doctor. Fundholding has already stimulated some practices to bring services to patients rather than send patients to hospital, and this trend seems set to continue. It is important to pool resources, not only within practices but among other practices in the area—joint action will increase the ability to improve the services for patients. If general practitioners take the opportunity to gain control of the changes the morale of the profession should improve.

The work of general practitioners has not changed greatly over the years. Fewer home visits are made now than previously, but the pattern of morning surgery followed by visits, paperwork, and evening surgery has endured for many years. Such familiarity has benefits but also threatens to stifle innovation. The financial security and tenure of general practitioners offers no incentive for progress[1] but despite this innovations have been and continue to be made. This article looks at evolving aspects of practice and their implications. The new roles I shall consider are the general physician in the community, the epidemiologist, the entrepreneur, the networker, and the defensive general practitioner.

The general physician in the community

The general physician in hospital practice is a thing of the past.[2] Higher training as a senior registrar produces an expert in a narrow field, and general experience is not likely to increase by shortening specialist training as outlined in the Calman report.[3] General practitioners who offer fewer services make more complaints about the number of consultations for trivia than those who offer more services,[4] and in the 1980s it was claimed that they had restricted their repertoire with few doing "very much with their hands as far as treatment is concerned."[5] If general practitioners develop the skills and enthusiasm to be general physicians in the community they might solve the problems of consultant overspecialisation and general practitioner boredom.[2 6 7] General practitioners' time could be freed to take on this role by developing the skills of other members of the primary health care team[8] and, in particular, using nurse practitioners to treat minor illness.[6]

Geoffrey Marsh, a general practitioner in Teesside, was one of the pioneers who employed a practice nurse before the 1966 charter made it economic to do so.[9] The nurse's role in his and many other teams has since been refined.[10] He believes that "Society has to develop a conventional wisdom of using a health professional who doesn't earn as much as a doctor. In the United States nurse practitioners became cheap alternatives to doctors, decided they wanted to be paid as much as doctors, and have now been virtually abandoned."

The minor illness nurse in Marsh's surgery, already an experienced practice nurse, sat in with one of the doctors for a year before taking on the role. The nurse decides what treatment is necessary but has to approach a doctor for a prescription, so a check takes place. "Doctors aggrandise medicine and their own role," Marsh told me. "Our patients love the nurse, availability is more important than the highest expertise. If the patient is seriously ill the nurse can get the doctor to see him or her straight away. The doctor is freed to deal with serious illness." Marsh has clearly taken great