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Fludrocortisone in the treatment of systemic hypotension in primary open-angle glaucoma patients

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Abstract

Background: Fludrocortisone is a potent mineralocorticoid, which has no known direct vasoactive properties, and is the first-line drug for treatment of orthostatic hypotension. The present study evaluated the systemic hemodynamic effects of fludrocortisone treatment in glaucoma patients. *Patients and methods:* A retrospective analysis of the charts of glaucoma patients of the University Eye-Clinic Basel was performed. Twenty-two patients with open-angle glaucoma under treatment with fludrocortisone were selected. The selected patients had one 24-h blood pressure recording immediately prior to treatment with fludrocortisone and one recording at least 2 months after starting the treatment. Parallel to blood pressure recordings, diurnal intraocular tension curve recordings and visual field testings were carried out. In addition, twelve patients also had nail-fold video-capillaroscopy. *Results:* IOP and visual fields remained stable. The average values for all systemic blood-pressure readings showed an improvement in the follow-up compared to primary examination. Mean (±SD) night-to-day ratio ('nocturnal dips') of systolic, diastolic and mean arterial blood pressure decreased from 13.6 ± 4.3%, 16.9 ± 5.2% and 15.9 ± 3.5%, respectively, to 9.9 ± 5.9% (p=0.01), 13.2 ± 4.3% (p = 0.044) and 11.7 ± 3.9% (p = 0.0004). Baseline capillary blood-flow velocity increased and capillary blood-flow standstill time after cold provocation decreased significantly under fludrocortisone therapy. *Conclusion:* Hemodynamic parameters show a tendency towards improvement in a magnitude which might be of clinical relevance.

Introduction

Microcirculatory alterations have been suggested as potential risk factors in glaucomatous optic neuropathy [1]. Intraocular pressure still remains the major predictor of future glaucomatous damage [2], and also contributes to glaucomatous damage in normal-tension glaucoma patients [3–6]. Nevertheless, a higher propensity for microvascular dysregulation has been found in glaucoma patients without increased intraocular pressure [7]. Low systemic blood pressure has been suggested to be a risk factor for glaucomatous damage [8]. Glaucoma patients without increased intraocular pressure as well as glaucoma patients who show progressive damage despite therapeutically normalized intraocular pressure have been demonstrated to have a lower average and nocturnal systemic blood pressure compared to normals [9]. Furthermore, nocturnal arterial hypotension occurs more often in patients with glaucomatous optic neuropathy [10].

Therapeutic modalities in glaucoma patients are limited to decreasing intraocular pressure. Although calcium-channel blockers might be helpful in treating ocular vasospastic syndrome [1], treatment of glaucoma with calcium-channel blockers has shown variable success, including the most recent studies [11–20]. Even less is known about the treatment of low blood pressure in glaucoma. Indeed, no studies have evaluated possible treatment modalities in glaucoma patients with low blood pressure. Findings demonstrating a strong association between low-perfusion pressure and the prevalence of primary open-angle glaucoma suggest, however, that in addition to decreasing intraocular pressure, glaucomatologists would be well advised to increase blood pressure in patients with systemic hypotension [21]. This can

be achieved in some patients by increased physical activity or increased salt intake. In more difficult cases, it has been suggested that fludrocortisone might be helpful [22]. Because glaucoma patients often demonstrate vascular dysregulation, and because such phenomena are statistically associated with systemic hypotension [23], directly vasoconstrictive substances should be avoided in the treatment of systemic hypotension in glaucoma patients [22, 24, 25]. Fludrocortisone is the firstline drug for treatment of orthostatic hypotension [26–28]. This drug has no known direct vasoactive properties. It is a potent mineralocorticoid with a mechanism of action which is believed to be sodium retention; this in turn leads to fluid retention and plasma expansion. A full pressor action usually develops within two weeks [26–28]. The purpose of the present study was to evaluate the systemic hemodynamic effects of fludrocortisone treatment in glaucoma patients.

Materials and methods

A retrospective analysis was performed of the charts of glaucoma patients attending the University Eye-Clinic Basel. Patients with open-angle glaucoma under treatment with fludrocortisone were selected. These were patients with progressive high-tension glaucoma despite medically well-controlled intraocular pressure (peak IOP readings below 21 mmHg on the last two diurnal IOP curve obtained prior to baseline measurement) or normal-tension glaucoma patients without increased intraocular pressure on at least 2 last diurnal intraocular pressure curves but with characteristic glaucomatous optic neuropathy and visual field defects. The visual field progression was defined as the increase in visual field mean defect (MD) of at least 3 dB during the pre-study period, namely, from the stabilization of IOP below 20 mmHg under topical therapy until the introduction of fludrocortisone, when the present study started. In all selected patients, fludrocortisone, 0.1 mg orally twice a week, had been prescribed because physical activity and increased salt intake alone had failed to improve systemic hypotension satisfactorily. Systemic hypotension was originally defined by at least two successive systolic blood pressure recordings under 110 mmHg for men (100 mmHg for women) and/or diastolic under 60 mmHg (both genders) using the 24h-blood pressure monitoring results. Patients with systemic hypotension due to over-treatment of systemic hypertension were excluded. Tenets of the Declaration of Helsinki were followed.

A total of 22 (15 females, 7 males) glaucoma patients were included in this analysis. The mean (±SD) age of these patients was 61.7 ± 10 9 years and the follow-up period ranged from 2 months to 28 months. During this observation period, neither topical nor systemic medications were altered.

The selected patients had to have one 24-h blood pressure recording, diurnal tension curve measurement and visual field testing immediately prior to treatment with fludrocortisone and the matching follow-up examinations at least 2 months after starting the treatment.

Diurnal tension curves were obtained by means of Goldmann applanation tonometry, with five readings over 24 h (at 6h, 8h, 11h, 16h and 21h) which were used to calculate the mean values for the baseline and the follow-up examination. Visual field testing was performed by means of Octopus program G1, and visual field mean defects prior to treatment and after the follow-up period were compared. Both IOP and visual field mean defects were calculated as the means for the right and left eyes, and both eye values entered the further analysis.

Blood pressure was monitored for 24 h with a Profilomat (Roche, Basel, Switzerland). This device measures the blood pressure automatically, on the same principle as the conventional mercury sphygmomanometer, with a cuff and a microphone. The interval between individual measurements can be preselected, and blood-pressure readings are recorded on a data processor. Measurements were performed every 30 min during the day (from 8 a.m. to 10 p.m.), and every 60 min during the night (from 10 p.m. to 8 a.m.). In both baseline and follow-up examinations the individual means of systolic and diastolic blood pressure were computed for day and night time, and for the entire 24-h period. In addition, the single lowest systolic and diastolic blood-pressure readings were identified. Mean arterial blood pressure (MABP) was calculated using the formula: MABP = DBP + 1/3(SBP-DBP), where DBP is diastolic blood pressure and SBP is systolic blood pressure. Night-to-day ratios (‘dips’) of the systolic, diastolic and mean arterial blood pressure were calculated using the general formula: 100 × (1 – night mean/day mean).

Twelve patients (8 females and 4 males), out of total of 22, also had video nail-fold capillaroscopy in parallel with other examinations. In these patients, video nail-fold capillaroscopy had been per-

formed prior to and after initiation of fludrocortisone treatment. Furthermore, in these patients, the 24-h systemic blood-pressure recordings and capillary microscopy were always performed on the same days. The methodology of video nail-fold capillaroscopy has been described previously [7]. Briefly, after determination of baseline blood-cell velocity, the skin area was cooled by blowing decompressed carbon dioxide at approximately −15 °C over the nail-fold. In cases where the blood flow ceased during local cooling, the duration of the blood flow standstill was measured for each capillary in seconds. The mean flow arrest time of all the capillaries measured was calculated.

The potential systemic side-effects of fludrocortisone therapy were analyzed using the history and data from the general physical and laboratory examinations (edema, headache, congestive heart failure, electrolyte perturbations – especially hypokalemia). Results of serum potassium level laboratory measurements were available for 11 out of 22 patients.

The changes in IOP, visual field mean defect and systemic blood-pressure parameters, namely 24-h mean and the lowest systolic and diastolic pressures, and night-to-day ratios of systolic, diastolic and mean arterial blood pressures, were assessed by means of paired t-test among the 22 patients. The changes in video nail-fold capillaroscopy were analyzed by means of paired t-test among the 12 patients who had undergone two examinations of their vasoreactivity.

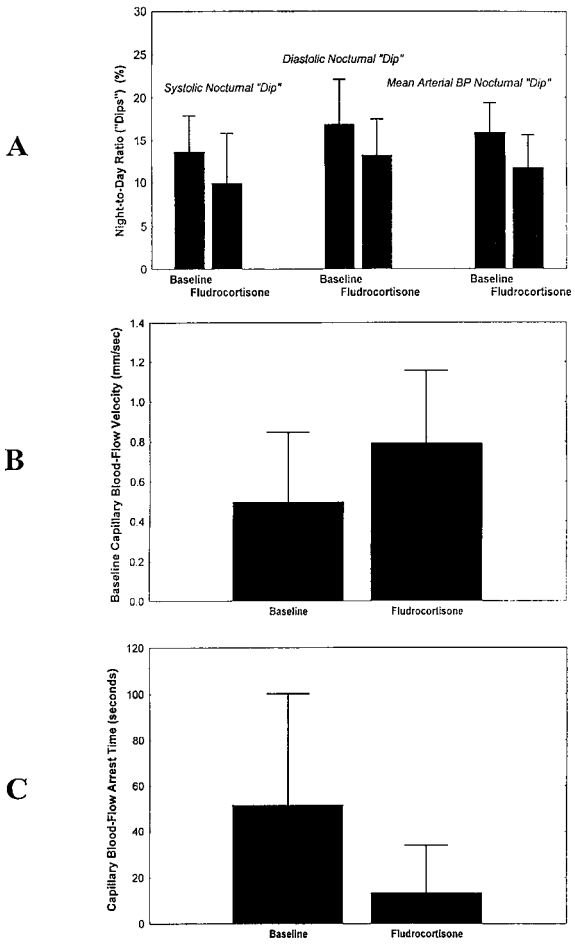

Figure 1. (A) The night-to-day ratios [100 × (1 – night mean/day mean) %] of systolic, diastolic and mean arterial pressure decreased significantly under fludrocortisone treatment (p-values 0.010, 0.044 and 0.0004, respectively). (B) Baseline capillary blood-flow velocity increased significantly under fludrocortisone treatment (p = 0.023). (C) Capillary blood-flow standstill time was decreased significantly under fludrocortisone treatment (p = 0.0078).

Results

The overall mean IOP increased from 16.1 mmHg to 16.7 mmHg, and visual field mean defect slightly decreased, from 7.2 dB to 7.1 dB. These changes were not statistically significant (p-values 0.12 and 0.79, respectively).

The average values for systemic blood-pressure parameters on baseline and follow-up examinations are given in Table 1. Night-to-day ratios (‘dips’) of systolic, diastolic and mean arterial blood pressure all decreased significantly (Figure 1A). The average values for all systolic and diastolic blood-pressure readings showed an increase in the follow-up compared to baseline examination. Changes in mean and the lowest systolic blood pressure over a 24-h recording period reached statistical significance.

Twelve patients had video nail-fold capillaroscopy under cold provocation. Baseline examination showed a mean (±SD) capillary blood-flow velocity of 0.49 ± 0.35 mm/second. In the follow-up examination, the mean (±SD) capillary blood-flow velocity was 0.79 ± 0.36 mm/second. The difference between these two examinations was statistically significant (Figure 1B; p = 0.023). The mean (±SD) capillary blood-flow standstill time was 51.54 ± 48.58 seconds on primary examination. The mean (±SD) capillary blood-flow standstill at the follow-up visit was 13.38 ± 20.46 seconds. This difference was also statistically significant (Figure 1C; p = 0.0078).

Serum potassium levels were 4.12 ± 0.53 mMol at baseline, and 4.0 ± 0.12 mMol at follow-up ex-

Table 1. Blood pressure parameters prior to and under treatment with fludrocortisone

	Baseline examination (±SD)	Follow-up examination (±SD)	t-test (p-value)
Mean systolic BP	108.7 ± 8.9 mmHg	111.7 ± 8.1 mmHg	0.032
Mean diastolic BP	73.2 ± 7.4 mmHg	74.7 ± 9.3 mmHg	0.271
Lowest systolic BP	79.6 ± 10.1 mmHg	86.1 ± 11.7 mmHg	0.019
Lowest diastolic BP	55.1 ± 9.2 mmHg	55.7 ± 10.2 mmHg	0.738
Night-to-day SBP	13.6 ± 4.3%	9.9 ± 5.9%	0.010
Night-to-day DBP	16.9 ± 5.2%	13.2 ± 4.3%	0.044
Night-to-day MABP	15.9 ± 3.5%	11.7 ± 3.9%	0.0004

BP = blood pressure; night-to-day SBP, DBP, MABP = night-to-day ratios of systolic, diastolic, mean arterial blood pressure calculated by the general formula: 100 × (1 – night mean/day mean) %.

amination (p = 0.61), based on the laboratory data from 11 patients. Furthermore, no adverse effects were observed in anamnestic and general physical examination data in any of the 22 patients.

Discussion

This retrospective analysis of patients treated with fludrocortisone at the University Eye-Clinic Basel, suggests that systemic hypotension can be improved with fludrocortisone in glaucoma patients. In addition to improvement in systemic hypotension, 12 patients showed an improvement in microvascular blood flow. This was demonstrated by an improved capillary baseline blood flow and, on average, a decrease in capillary blood-flow standstill time after cold provocation. No significant change was observed either in IOP or in visual field mean defect during the follow-up period.

Treatment modalities for vascular alterations in glaucoma patients are scarce. Especially for cases of systemic hypotension, no treatment has been evaluated in a controlled study. Although fludrocortisone has been suggested as a potential treatment modality in glaucoma patients [29], whether such a treatment would in the long-run really be beneficial for glaucoma patients remains to be confirmed in a prospective study.

The present results suggest that fludrocortisone improves the hemodynamic status of glaucoma patients with systemic hypotension. Although the increase in mean systolic and diastolic blood pressure was of little magnitude, the overall night blood pressure ‘dips’ reduction and the increase in the lowest systolic blood pressure reading were more substantial and possibly of clinical relevance. It is particularly the nocturnal blood pressure ‘dips’ that have been implicated as the risk factor for glaucoma and the progressive glaucomatous damage [8, 10]. In addition, it seems that fludrocortisone might improve other aspects of microcirculatory disturbances such as capillary vasospastic reactions. Albeit the follow-up period was in some cases as short as 2 months, the observed overall stability of visual fields and IOP is encouraging. However, this is a retrospective analysis, and the results need to be confirmed in a prospective study.

Vasospastic patients often show systemic hypotension. Whether the relationship between vasospasm and systemic hypotension is incidental remains to be clarified. Several studies, however, suggest that these phenomena might be related [30, 31] and may in fact be due to same underlying vascular dysregulative alteration [32]. The present finding of a parallel improvement in systemic hypotension and in capillary vasospastic reaction to cold provocation also suggests that, indeed, these two entities might well be related to some common pathogenesis. At this point, no further explanation can be offered, i.e., as to whether fludrocortisone might also have the direct vascular effect on the capillary bed, and would this effect take place only in a particular group of patients.

Systemic hypotension in these patients is probably not a transient phenomenon, but rather a permanent, life-long problem. With the prolonged use of fludrocortisone, adverse reactions may occur, such as hypertension, edema, headache, weight gain, congestive heart failure, electrolyte perturbations, infection masking, interaction with other drugs (oral anticoagulants, antidiabetic agents, aspirin, barbiturates etc.), posterior subcapsular cataract, increased intraocular pressure [26–28, 33, 34]. Noting again that the follow-

up period was in some cases quite short for any valid conclusion with regards to this issue, it is nevertheless indicative that we observed no side-effects in any of the patients. The average IOP increase from 16.1 mmHg to 16.7 mmHg is neither statistically significant nor of clinical relevance. A possible explanation is that the usual initial dose of fludrocortisone in cases of moderate and severe orthostatic hypotension is two to three times higher than the dose applied in the present cohort. Still, in spite of sub-dosing, fludrocortisone therapy did produce systemic hemodynamic improvement.

The present study, being retrospective, has the obvious flaw of lacking the control placebo- or non-treated group. The follow-up examination time varies from 2 to 28 months rendering the results perhaps less reliable, especially in view of the fact that it sometimes takes up to 2 months for definite effects of fludrocortisone therapy to occur [33, 34]. However, the latter statement refers to the situation where an increase in dosage regimen is warranted, and it is, therefore, necessary to wait for the new dose to take effect. In this study no dosage increase took place in a deliberate attempt to avoid undesirable side-effects. More recent studies on fludrocortisone [26–28] confirm that 2–3 weeks are sufficient for a full pressor action to develop with the given dosage regimen. Other recent studies, however, utilizing a placebo-controlled, cross-over, prospective study design with a similar number of patients as in the present study, failed to demonstrate any beneficial effect of the low-dose fludrocortisone therapy, e.g., in chronic fatigue syndrome patients [35]. A somewhat different response to low-dose fludrocortisone therapy in our study may indicate, besides differences in methodology, that glaucoma patients, as defined here, represent a unique cohort of patients. Systemic hemodynamic parameters did show a tendency towards improvement in a magnitude which might be of clinical relevance, and no adverse effects were observed. The observed improvement in vasospastic tendency, demonstrated by means of capillary microscopy, should also not be neglected when conclusions are drawn from the present data. The episodes of sub-threshold perfusion, probably taking place during night sleep, may be predominantly caused by perfusion pressure falling below the critical level (due to systemic hypotension), but it is also plausible that increase of blood flow resistance due to vasospastic propensity could also have taken part in such events, leading ultimately to accumulation of glaucomatous damage. Thus, the observed improvement may in the long-run be of the same importance for withholding the damage progression as the improvement in systemic blood pressure. Whether such positive tendencies might prove reliable with the larger number of patients in a prospective, placebo-controlled study, and whether such a treatment might also be relevant for the long-term preservation of the visual field, is an aspect which needs to be assessed by further studies.

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