Antihypertensive treatment with diuretics: antediluvian or up to date?

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Introduction: the decline of the thiazides

Thiazide diuretics were among the first drugs able to lower blood pressure with minimal side-effects in a large proportion of the hypertensive population. Hence they were advised as the mainstay of antihypertensive treatment and were used in all large-scale trials [1] which showed beneficial effect of blood pressure lowering on cardiovascular morbidity and mortality. Despite this success story, the use of diuretics has rapidly declined during the past 15 years. From 1982 to 1988 prescription of diuretics in elderly hypertensives decreased from 59 to 33% in the USA, despite growing evidence of their benefits, particularly in this age group, during the same period [2]. Most probably this trend persisted in all patient groups during the following years. As an extreme example, the last thiazide-type diuretic (chlorothalidone) was taken off the market in Turkey in 1992.

Is this development justified, and if not (as is my personal opinion) what should be the place of diuretics today? Before discussing their relative drawbacks and merits, it is essential to review very briefly the reasons for their premature falling into disgrace.

Events influencing prescription behaviour of diuretics

De-emphasis on salt restriction

There is abundant epidemiological and experimental evidence that salt consumption plays a pathogenetic role in the development of hypertension. Overenthusiastic proposals for salt restriction as a general health measure met with equally unbalanced reactions, such as: 'Salt has only small importance for hypertension' [3]. Some authors even implied that salt restriction may be a health hazard [4]. Although this assertion was adequately rebutted [5] there is no doubt that such claims also influence the attitude towards diuretics that derive their effect from creating a slightly negative NaCl and volume balance [6].

'Low renin hypertension is not harmful'

It has been repeatedly claimed that cardiovascular morbidity is higher in patients with elevated renin despite similar blood pressure levels [7] and a suggested scheme was drawn up showing low renin, vasodilatation, and no complications at one extreme. An editorial [8] suggested that 'some hypertensives may not need any treatment at all' and questioned the value of diuretics because they elevate plasma renin. Although the concept of 'vasodilative hypertension' was never confirmed, the influence of such an authoritative statement may persist.

Failure of large intervention trials to show decreased cardiac mortality

Despite the impressive reduction of strokes, reduction of coronary events was not achieved or failed to reach significance in most trials in mild-to-moderate hypertensives. This led to the speculation that the metabolic side-effects of diuretics used in these trials were counterproductive with regards to coronary disease [9].

Subsequent meta-analysis, however, showed that there was still a significant decrease in coronary events in these trials [10], albeit less than expected. Yet the question what should be 'expected' is not a simple one. One review [11] concludes that there was a 'clear relative therapeutic failure' and accused an author who questioned the supposed negative effect of diuretics [12] of having disregarded relevant data to the contrary. Others remark that the duration of the trials was too short and so the fact that reduction of coronary events failed to meet expectations was not surprising [2]. In addition, more recent studies in elderly patients using low-dose diuretics showed a clear decrease in cardiac deaths. Thus patients considered particularly at risk also showed the clearest benefit [13]. These findings illustrate the fallacy of using 'surrogate end points' [14].

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New drugs

As suggested above, the arrival of new effective antihypertensive drugs, in particular converting-enzyme inhibitors and calcium antagonists are probably the main reason that diuretics have fallen into disuse. In each of these classes a large number of different brands are marketed, sometimes slightly different, more often identical in their mode of action. The research devoted to them creates an avalanche of articles which do not excel in originality. Although there are many truths in them, the overall result is half-truth, as the sheer quantity of identical information creates a bias. Diuretics, their patents long expired, are hardly mentioned any more. It is not without reason that ‘the case against thiazide diuretics has been conducted almost entirely outside the columns of peer-reviewed medical journals. Their supposed risks have been broadcast in countless advertisements of new drugs as well as in numerous symposium proceedings and monographs, all sponsored by the pharmaceutical companies [12].

In order to get a more balanced view, let us review what is known about the actions and side-effects of diuretics.

Side-effect profile of diuretics

Volume depletion and hyponatraemia

The hypotensive action of diuretics is based on their ability to decrease extracellular volume. This arouses a number of counterregulating mechanisms, one of which is stimulation of the renin–angiotensin–aldosterone system. This limits their action by increasing salt and water reabsorption in tubular segments proximal and distal to the site where they block Na reabsorption. The increased volume reabsorption by the proximal tubules decreases the flow to distal parts and limits the ability to excrete ‘free water’, while excessive angiotensin levels may stimulate thirst, thus setting the stage for development of relative water excess and hyponatraemia. While diuretic treatment is often mentioned among the causes of hyponatraemia [15] it is clear that this will only occur with doses much higher than needed for blood-pressure control, or (probably more often) when other volume-depleting factors like diarrhoea are superimposed.

Other ‘proximal’ effects

Increased volume reabsorption is also associated with increased reabsorption and decreased urinary excretion of calcium, lithium, and uric acid. The former effect has been used to decrease the number of kidney stones. Hypercalcaemia is not a common side-effect as other factors are dominating in the regulation of serum calcium levels.

Patients treated with lithium may develop serious lithium intoxication when given diuretics unless lithium dosage is adjusted.

Some increase in uric acid blood level is a constant ‘side-effect’ of diuretic use, even with small dosage [16]. Elevated uric acid levels are epidemiologically related to vascular damage and this was used as an argument against diuretics. However, it is well accepted today that a causal relationship does not exist.

The occurrence or aggravation of gout is a relative contraindication to diuretics. If they are needed still, decrease of uric acid levels can be achieved by adding uricosurics or allopurinol. Use of such agents only to decrease uric acid blood levels in the absence of symptoms is not recommended.

Potassium depletion

Thiazide diuretics temporarily increase K excretion and cause varying degrees of decrease in serum K levels. The magnitude of this decrease is clearly dose dependent and is also influenced by concomitant salt consumption.

The reason for this is the increased delivery of filtrate to the distal nephron in the presence of volume contraction which activates aldosterone-dependent K secretion in that tubular segment. The evidence that diuretics also cause potassium depletion is weak [9]. Probably, they decrease intracellular K stores by less than 5%, which may not be physiologically important. The decrease in serum K level was —0.16 mm/l with the lowest effective dose of bendrofluazide and increased stepwise to —0.45 when the dose was increased eightfold [16]. The possibility that such decreases stimulate cardiac arrhythmias and sudden death has been hotly debated and I have to refer to some in-depth reviews on this subject [9,11,12]. The most likely conclusions are the following:

Although the risks of diuretic-induced hypokalaemia, have often been based on uncritical extrapolation, there is circumstantial evidence that they may predispose to serious arrhythmias and sudden death. This is probably true for patients with cardiac disease, particularly when taking digitalis and in patients with prolonged repolarization times [11]. In addition many drugs in common use prolong Q-T interval. In that condition hypokalaemia may increase the risk for ventricular tachycardia ‘torsade de points’ [11].

Because these possible dangers are related to hypokalaemia and not to diuretic drugs themselves, they can be prevented by adding K-sparing drugs.

Magnesium depletion

Magnesium excretion is acutely increased by diuretics. The mechanism is not clear as Mg is mainly reabsorbed in the loop of Henle. Few studies have been devoted to this subject and most of them are poorly documented and circumstantial. Modest decreases in serum Mg levels after thiazide diuretics have been reported in some but not in other studies. Evidence of Mg depletion is even less convincing and the clinical significance is obscure [9].
Glucose metabolism

Glucose tolerance is decreased by the use of diuretics. This effect is probably related to the decrease in serum K levels [17]. However only 1% of diuretic treated patients develop clinical diabetes [18].

Another phenomenon is the fact that insulin resistance (often present in hypertensive patients) is further increased by diuretics. Although the claim that insulin resistance causes hypertension [19] has been shown to be unfounded [20], this has been used as an argument against diuretic treatment.

These considerations gain more importance in diabetic patients. Despite the fact that extracellular fluid has been found to be expanded both in type I and type II diabetes, diuretics [21] are often considered contraindicated in diabetic patients. There are no long-term studies on diuretic monotherapy, but nearly all investigations showing beneficial effect of blood-pressure lowering on renal function and prognosis in type I diabetes included diuretics [22,23], although this is often not mentioned in the summary. No mention is made of worsening of glucose control. In a meta-analysis of 93 papers on the effect of hypertension treatment on diabetic proteinuria [21] diuretics (with or without beta-blockers) were shown to be more effective than calcium antagonists in decreasing proteinuria. The author also stated that high doses of diuretics 'can impressively improve hypertension resistant to other drug combinations', but nevertheless cautioned against the use of diuretics.

Indeed one uncontrolled retrospective study [24] has claimed that diuretic treatment increased cardiovascular mortality 3.8-fold (!) in diabetic patients. Although most reviewers express doubts on the validity of these unexpected results, there is a general tendency not to use diuretics as monotherapy 'until more evidence (prospective studies) becomes available'. In the given circumstances it is questionable whether such a trial will ever be performed. This issue, like others discussed in this review, is nicely illustrated by the Turkish proverb: 'A fool threw a stone in a pit, and 40 wise men could not get it out'.

Lipid metabolism

There is no doubt that diuretics cause increases of total cholesterol, LDL cholesterol, and apolipoprotein B [25]. These changes are dose dependent and probably related to volume depletion [26], although the observation that they are not seen after spironolactone [25] suggests a relationship to potassium. According to some studies triglycerides may also increase. The observed changes are generally mild, none of the trials showing more than 0.27 mmol/l change for cholesterol [12]. Studies lasting more than 1 year showed either no change or some decrease [27], although in the HAPHY trial, serum lipids decreased after discontinuing diuretics. Thus it cannot be excluded that their levels would be lower when treated with placebo. Yet these data illustrate how much widespread suggestions of adverse effects of diuretics have been exaggerated.

Impotence

This is a condition for which it is notoriously difficult to obtain objective data. While its frequency is underestimated unless specifically asked for, it may also be erroneously attributed to whatever medication is taken. Yet there is no doubt that thiazide diuretics can (reversibly) cause impotence. The pathophysiology is obscure. A recent investigation [28] reported 'serious sexual dysfunction' in 21% of diuretic-treated men against 9% in a control group. Another study [29] noted erection difficulties in 17% of men treated with chlorothalidone over 4 years, against 10% in those taking beta blockers and 16% in a placebo group! It seems that the complaint is also dose dependent, as a study using a lower dose [16] reported no difference with other hypotensive drugs.

Antihypertensive efficacy and dose–response curve

There is general agreement that the antihypertensive effect of diuretics is roughly equivalent to that of other hypotensive drugs. They usually do not lower blood pressure in normotensive subjects and an important percentage of hypertensive patients is also resistant to their effects.

Without going into details it may be said that the reason for this 'non-responsiveness' is the activation of counterregulatory systems, mainly the sympathetic and renin–angiotensin systems.

Elevation of the dose, while decreasing body fluid volume, excessively stimulates renin and results in no further decrease in blood pressure. It has lately been shown that previously used doses were higher than necessary and greatly enhanced side-effects. This flat dose–response curve was elegantly shown for bendrofluzide [16]: while 1.25 mg decreased BP by 12.7/9.8 mmHg, 5 mg per day caused negligible further decrease, and the highest dose (10 mg) gave an additional drop of 4.3/1.0. The percentage of 'responders' also did not increase. This study also demonstrated that maximal response is only reached after 10 weeks of treatment. This is related to secondary adjustments, which partly restore the initial volume decrease while peripheral resistance is lowered [31].

It should be remarked, however, that individual sensitivity to the salt excreting action of diuretics is diminished even with slight impairment of renal function such as occurs also with long-standing hypertension. In that case the dose–response curve shifts to the right and higher doses are required.

Monotherapy

It has recently become fashionable to stress the need for 'individualized' treatment [32], as if such a concept never existed before. However, what is really meant is (sequential) monotherapy. The underlying idea is that there are now so many therapeutic options that it is
possible to find an effective drug for every patient and that side-effects will be less than with combination treatment [33].

Unfortunately both assumptions are unproven and most probably untrue. It is astonishing though, that hardly any systematic attempt has been made to compare the reactions of individuals to different drugs. Laragh et al reviewed 1486 reports published in English comparing the effect of two or more antihypertensive drugs [34]. In the majority, the drugs were given to different patients. From those who exposed their patients in a cross-over fashion to both drugs, the majority failed to give individual data. Only three of them did so and (as could be expected), showed some striking difference between individual responses. It has long been known that patients with low renin values are particularly sensitive to diuretics and others respond better to beta-blockers and converting-enzyme inhibitors. Yet this appears not to provide sufficient basis to lower blood pressure in all patients. Two recent trials again only investigated monotherapy in different groups. In one [33] investigating only male patients, the percentage reaching the goal (<95 mm diastolic) ranged from 42 for captopril to 59 for diltiazem. Hydrochlorothiazide (HTC) was successful in 46% and placebo in 25%. Low-dose HTC was associated with minimal biochemical alterations and the lowest rate of drug intolerance. Diltiazem was only successful in the highest dosage.

The TOMHS trial [27] of mild hypertension (both men and women, 20% blacks) reported only minimal differences in BP response and biochemical changes after 4 years of treatment between five different drugs. The diuretic group used low-dose (15–30 mg) chlorthalidone, which caused only a small decrease in serum K and increase in uric acid. Importantly, this group showed (together with acebutolol) the greatest improvement in quality of life. Chlorthalidone also caused the largest fall in left ventricular mass. The latter finding was confirmed by a recent meta-analysis [35], thus contradicting earlier claims that diuretics do not cause regression of cardiac hypertrophy. It was concluded [27] that the results support the most recent JNC-V recommendation [36] of diuretics and beta-blockers as initial drugs.

Taken together the available evidence indicates that low-dose diuretics form excellent treatment for those hypertensives who are responsive, particularly older patients and black people. The arguments in favour are ease of administration, flat dose–response curve, lack of side-effects and proven preventive effect. While some reviewers argue that ‘if we could do better, we should’ [11], we agree with a recent review concluding in these cases ‘thiazide-based therapy leaves no room for improvement’ [37]. However, thiazides are even more important as an indispensable part of combination treatment.

**Combination treatment**

Even in uncomplicated mild hypertension, good blood pressure control requires combination therapy in about half of the cases [38].

Because the hypotensive effect of diuretics is often limited by stimulation of the renin–angiotensin–aldosterone system (which also increases side-effects) it seemed logical to combine them with drugs that derive (part of their) action from inhibition of that system. Thus the combination of diuretics and beta-blockers was advised and successfully applied in most of the trials mentioned earlier. We showed [39] that in a group of ‘resistant’ hypertensive patients, diuretics and beta-blockers individually only caused a 10% decrease in blood pressure, while the combination was more than additive, decreasing BP by 30%. In a much larger trial [40] it was shown that diuretics combined with salt restriction and beta-blockers could normalize BP in more than 90% of (moderately severe) hypertensives. Such high success rates have to our knowledge never been reported with monotherapy or any other drug combination. Theoretically even better results may be reached when combined with converting-enzyme blockers which probably have some additional advantage of specific renal and cardiac protection. In addition they counteract hypokalaemia and related side-effects by lowering aldosterone levels. However, few investigations have been published on this subject.

In practice, treatment can be started with either of the two drugs, the other being added when insufficient response is obtained. Adding a converting-enzyme inhibitor (CEI) to a patient using diuretics carries some risk of excessive blood-pressure decrease. Thus starting with a CEI is better, but in that case some patients may continue to use that drug while monotherapy with a diuretic would suffice. However, as the combining of low-dose diuretics with low-dose CEI almost completely obliterates the side-effects with respect to lipids and glycaemia, this may be a rational therapy.

When hypokalaemia remains a problem a potassium-sparing drug or potassium supplement can be added, but it must be borne in mind that the potassium-sparing effect of combinations presently on the market is often not sufficient to completely restore normokalaemia. Maintenance of completely normal K levels may not be required in the majority of the patients.

It has been claimed that diuretics do not improve the hypotensive effect of calcium antagonists. This is surprising because these agents sometimes cause fluid retention. Other studies showed some effect, but less than additive, of combination with diuretics, (perhaps because of the intrinsic natriuretic activity of calcium antagonists) but less than with other drugs.

When the HAPHY trial, comparing a beta-blocker with a diuretic was started, I refused to participate because it was not permitted to combine these drugs in cases of no response, thus depriving many patients of the proven benefit of the combination. Some later clinical trials (e.g. [32]) are liable to the same ethical objection. The reason that combinations are not applied are probably: ‘embarrass de choix’ of available drugs, the emphasis on monotherapy, the lack of new trials in which they are applied [38], and last but not least the absence of mentioning combinations in all
advertisements. It is well known that the latter have more influence on physicians’ prescribing behaviour than do scientific articles and advisory committees [41].

Conclusions. Where do we stand today?

The negative aspects of thiazide diuretics have been greatly exaggerated during the past 15 years. Proof that they cause (relative) increase in cardiac morbidity and mortality has never been provided. Yet there is circumstantial evidence, that the hypokalaemia induced by them may increase the risk of dangerous cardiac arrhythmias under certain conditions.

It has been shown that many of their biochemical side-effects are lessened or abolished by lower dosage without losing the blood-pressure lowering action.

Monotherapy with diuretics is the simplest and cheapest way to achieve blood-pressure control in many hypertensive patients and is particularly effective in the older age group [42]. It has not been (and probably will never be) proven that in such patients any other single drug is superior. The fact that they are cheap is a definite advantage in many countries. Their main drawback (which they share with all other drugs) is that they do not achieve complete blood-pressure control in many patients. While some of these will respond well to other drugs the main question is not which single drug is superior, but what regimen is best in the long term. The suggestion that by sequentially trying out monotherapy, normotension can be achieved in all patients has never been substantiated. To achieve that goal combination treatment is necessary. There is a firm pathophysiological basis for combining thiazide diuretics with beta-blockers and converting-enzyme inhibitors, that potentiate each other’s hypotensive effects.

Advice to use diuretics has been called ‘voices of the past’ and ‘a large step backward’ [43]. I have tried to restore the balance by showing that not only in the ‘antideluvian’ but also in the modern era, antihypertensive strategy that does not include diuretics cannot be completely successful.

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