Seasonal dosage-dependent hypersensitivity to the angiotensin II receptor blocker, losartan. A case report and review

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SHORT TITLE: Monitoring Losartan Dosage in Hot Weather

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Abstract

Since it has been in clinical use for two decades, individual data permitting evaluation of the long-term treatment of hypertension with losartan, which blocks the dominant angiotensin-II receptor (AT_1R), should now be available. In the present case, by dosage adjustment according to daily home blood pressure (BP) readings, a mild degree of hypertension discovered during routine examination was kept in the 130/80 (mm Hg) range over an 11 year period (2003-2013). In the early years, control was achieved with 12.5 – 25.0 mg/day and dosage adjustment was seldom needed on a seasonal basis. However, on increasing to 50 mg/day, a profound downward adjustment to 0 – 12.5 mg/day was required in hot weather. The adjustment may have prevented recurrence of drug-induced postural hypotension and renal colic. Whether the adjustment facilitated an increased nocturnal BP, as suggested by some ambulatory BP studies, was not examined. A working hypothesis, consistent with animal experiments, is that under conditions of heat-stress (e.g. vascular dilation, salt loss), there is increased expression of a countervailing, losartan-insensitive, receptor subtype (AT_2R). By *lowering* BP in response to antiotensin-II, AT_2R would facilitate fine-tuning of the AT_1R-mediated vasoconstriction that supports BP when superficial veins dilate to enhance body cooling. This AT_2R activity might be sufficient to explain a small summertime BP dip found in normal human subjects whose Ang II levels are not increased. The dip would be greatly enhanced when Ang II levels were increased at higher losartan dosages. Close monitoring of losartan dosage may be necessary for those living in, or travelling to, geographical regions where temperatures are seasonally or continually high, and for those engaging in activities that involve such exposure (e.g. hot yoga, Turkish baths).

Introduction

Summertime declines in blood pressure (BP), both in normotensive and hypertensive subjects, have long been known.[1-5] However, the declines are small (e.g. 5-10 mm Hg) and are not known to relate to a particular form or dose of antihypertensive therapy. Furthermore, adverse cardiovascular events are of more concern in wintertime.[6] While analyzing data from a subject whose BP had been controlled for over a decade with losartan, a potentially dangerous, dosage-dependent, summer-time influence came to light. Given that this angiotensin-II receptor blocker (ARB) is now a treatment of choice for many millions of hypertensive subjects, among whom acute kidney injury (AKI) is becoming increasingly associated with ARB prescription,[7] it is unlikely that this is an isolated case.

Case Report

In August 1999, mild hypertension (circa 150/90 mm Hg) was discovered during routine physical examination of a healthy 60 year old biomedical researcher. Although his laboratory discovered a gene that regulated BP,[8,9] his primary research interests were in other areas. Nevertheless, he followed the course of his new condition with deep professional interest. This led to his authoring the present report.

Assuming the hypertension to be primary ('essential'), after a two month trial of chlorothiazide (25 mg/day), his physician prescribed losartan potassium (Merck, NJ, USA; 50 mg/day). The following reduction in BP (systolic sometimes down to 100 mm Hg as measured at home with a classic mercury sphygmomanometer), was accompanied by postural hypotension. In December 1999 the subject purchased an Omron digital BP monitor (HEM-712C) and stopped therapy. Apart from occasional travel periods (1-3 weeks), and forgetful 'misses,' readings were

taken at least once daily (usually both in early morning and late evening) at his home in Kingston, Ontario. The continuing accuracy of the instrument was ascertained by comparing readings with the classic device and with those obtained in the physician's office.

Having had an athletic youth, the subject's resting pulse had registered around 50/min for many years. His lifestyle was that of an academic workaholic – several hours a day at a computer interrupted by frequent brisk walks, and twice weekly runs (two km). Height and weight had remained relatively constant throughout adult life (currently 1.76 metres and 72 kg; BMI = 23.2). In the period of this study, indoor temperatures were regulated at around 22°C during cold weather. In summer months fans were employed and only short periods were spent in air-conditioned environments. While the present report focuses on the 2003-2013 period, a brief account of the first three years (2000-2002) provides relevant background.

2000-2002

In the year 2000, two one-month trials (Feb., Apr.) of daily losartan (25mg) with chlorothiazide (12.5 mg) resulted in progressive falls in day-time BP, with some systolic values (SBP) around 100 mm Hg (Fig. 1). Consistent with this, the subject experienced some dizziness on standing up abruptly. On cessation of these medications, BP values progressively returned to previous levels. In June, chlorothiazide alone (12.5 mg) had little effect. However, losartan alone (25 mg), taken at the height of summer (August, with environmental temperatures approaching 30°C), produced a progressive and more profound fall in pressure, with SBP values again below 100 mm Hg, and diastolic (DPB) values approaching 60 mm Hg. Shortly after cessation of therapy there was acute renal colic and blood pressure rose abruptly (Fig. 1). A ureteral stone observed on X-rays was presumed to have passed in the urine.

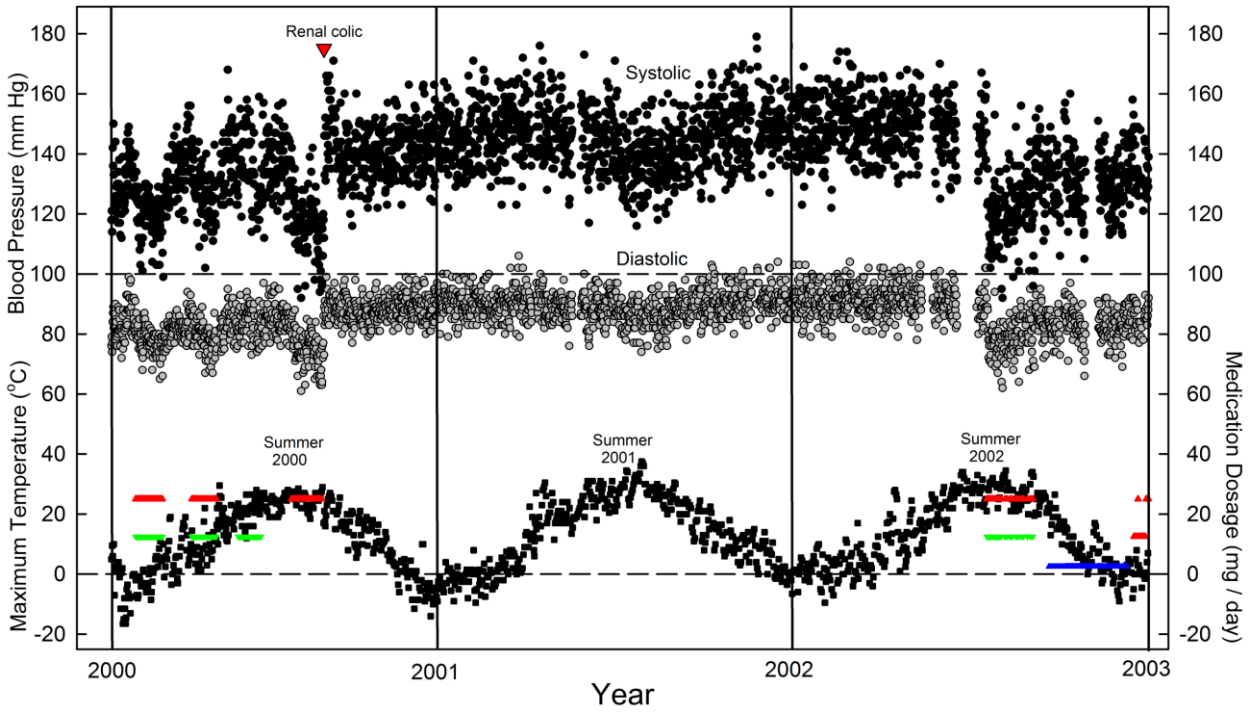

Figure 1. Daily variation in SBP (black circles) and DBP (grey circles) over a three year period, as related to (i) maximum daily environmental temperatures (small black squares) and (ii) periodic treatments at constant dosage with losartan (red triangles), chlorothiazide (green triangles) or ramapril (blue triangles). At the far right, the two rows of red triangles mark the initiation of an eleven year period (2003-2013) where the day-to-day dosage of losartan was varied. Renal colic in the year 2000 is marked by a large red triangle. Home BP measurements were usually taken 2-3 times a day – in the early morning, in the early afternoon, and in the evening. All measurements are directly plotted. Gaps indicate periods of travel when readings were discontinued. Since records of temperature values for the subject's lakeside city (Kingston, Ontario) did not become available until 2008, values for a location 24 km north (Hartington) were employed. The latter tends to be 2-3 degrees cooler/hotter in winter/summer than Kingston.

In view of the timing, and the subject not having previously experienced renal colic, it was considered possible that stone formation had been facilitated by hypotension. Indeed, there is now increasing awareness that AKI can follow ARB medication in a range of settings, particularly during acute hypovolemic illness.[7] Medications were avoided for the next two years and pressure values remained relatively constant in the 150/90 range (Fig. 1). However, in the summer of 2001 there was a small dip, which correlated inversely with environmental temperature (Fig. 2).

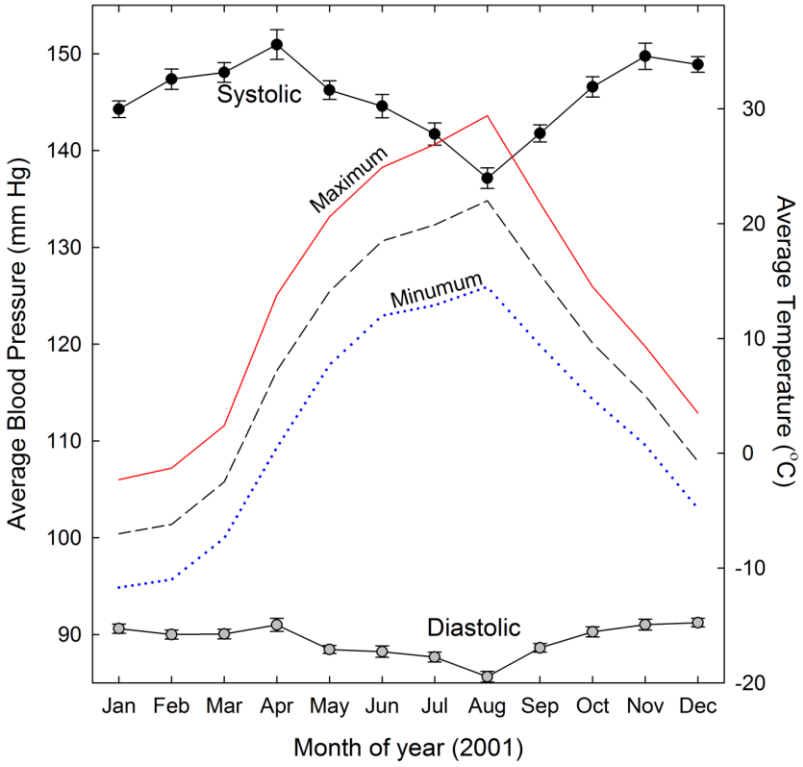

Figure 2. Seasonal variation in SBP and DBP in absence of hypertensive medication. Daily values for each month in the year 2002 (as in Figure 1), are averaged and plotted with standard errors. Corresponding monthly average temperature values are shown without symbols (*maximum*, continuous red line; *average*, dashed black line; *minimum*; dotted blue line).

In the summer of 2002 mild hypertension was confirmed by one session of 24 hour ambulatory BP (ABP) monitoring and, for a six week period (beginning in the last week of July), daily combination therapy with losartan (25mg) and chlorothiazide (12.5 mg) was resumed (Fig. 1). Again, there were extreme declines in pressure values and some minor dizzy episodes. BP was controlled more satisfactorily with the angiotensin convertase (ACE) inhibitor, ramipril (2.5 mg/day; late September to early December). However the subject experienced a persistent dry cough, so ramipril was discontinued. Although there had been some dry coughing with losartan, therapy with losartan alone was resumed at the end of December 2002 (rows of red triangles at extreme right in Fig. 1). Dosage was adjusted daily according to BP readings. This proved satisfactory for the next eleven years, despite some dry coughing.

2003-2013

With various combinations of half (12.5 mg) and whole (25 mg) tablets, daily losartan dosage was varied over the range, 0, 12.5, 25, 37.7 and 50 mg, taken either in the early morning or, from Dec 2010 onwards, split between mornings and evenings (under guidance of BP readings taken at the same times). Further fine adjustment was attempted by trying to maintain regular dosage patterns – e.g. 12.5 mg, 25 mg, 12.5 mg, 25 mg, etc.. As before, standard blood and urine tests remained within normal ranges, except that on occasions creatinine levels approached high normal. Apart from weekly sildenafil citrate (50 mg), losartan was the sole medication.

For the first four years (2003-2006) the required average losartan dose was 16mg/day, rising to 18mg/day for the next three years (2007-2009). Thereafter, the average requirement rose from 19 mg/day (2010) to 41 mg/day (2013). An example of the ability to fine-tune day-time BP readings over the 2003-2009 period is shown for the year 2007 (Fig. 3). With relatively constant losartan dosages (average 18mg/day), blood pressure readings were maintained at acceptable values

(130/80 mm Hg). There was generally no need to make special dosage adjustments in the hot summer season.

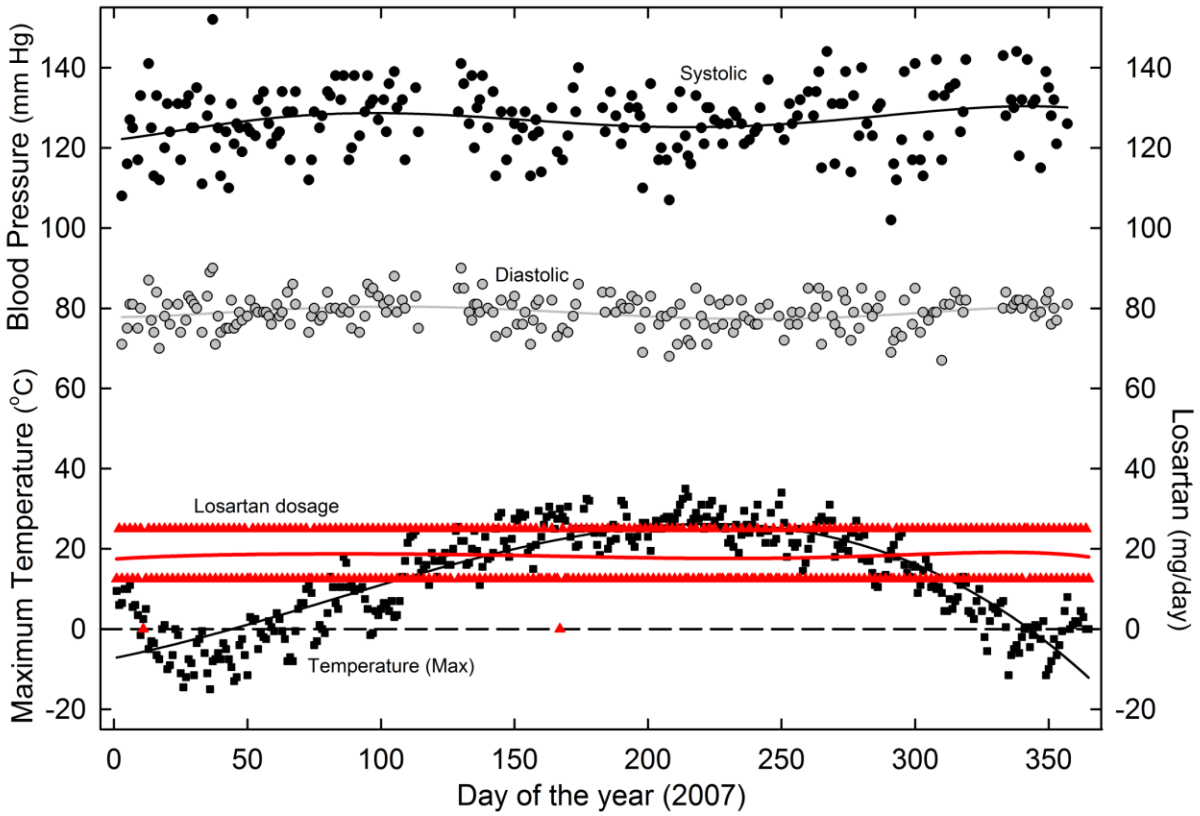

Figure 3. Daily variation in SBP and DBP in 2007, as related to (i) maximum daily environmental temperatures and (ii) varying losartan dosage. Home BP measurements were usually twice daily – in the early morning and late evening – and these values were averaged for plotting. Least-squares regression (sixth order) polynomial fits to the points are shown as continuous lines (the fit is third order for the red temperature line). For other details see Figure 1.

These same BP values were sustained in the 2010-13 period. However, when, for some unknown reason, the total losartan requirement *increased*, an extreme *downward* dosage adjustment became necessary in the summer season. This is shown for the year 2012 in Figure 4.

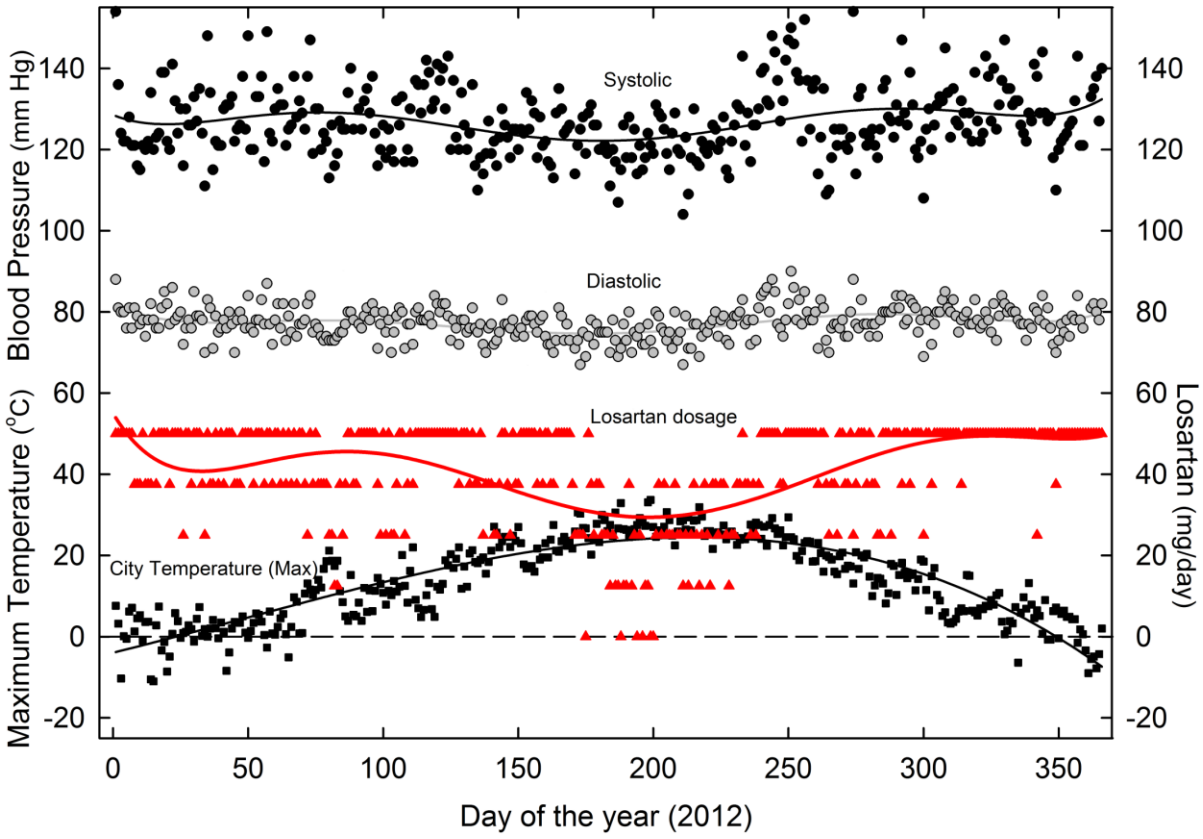

Figure 4. Daily variation in SBP and DBP in 2012, as related to (i) maximum daily environmental temperatures and (ii) varying losartan dosage. For details see Figures 1 and 3.

A monthly break-down of losartan requirements for the entire eleven year period is shown in Figure 5. At the lower doses employed between 2003 and 2009 (average 16-18 mg/day), usually no special adjustment was needed for the summer season. In 2006 (a particularly hot year), an adjustment was needed, but it was minor. The plot for 2011 was distinctive. Following a small increase in losartan requirement in December 2010, in the early part of 2011 the requirement was high, but decreased to previous values during spring and summer. However, in the latter part of the year as environmental temperatures declined, there was a sharp increase in losartan

requirement. Subsequently (2012, 2013), the extreme seasonal requirement for downward adjustment of losartan dosage emerged.

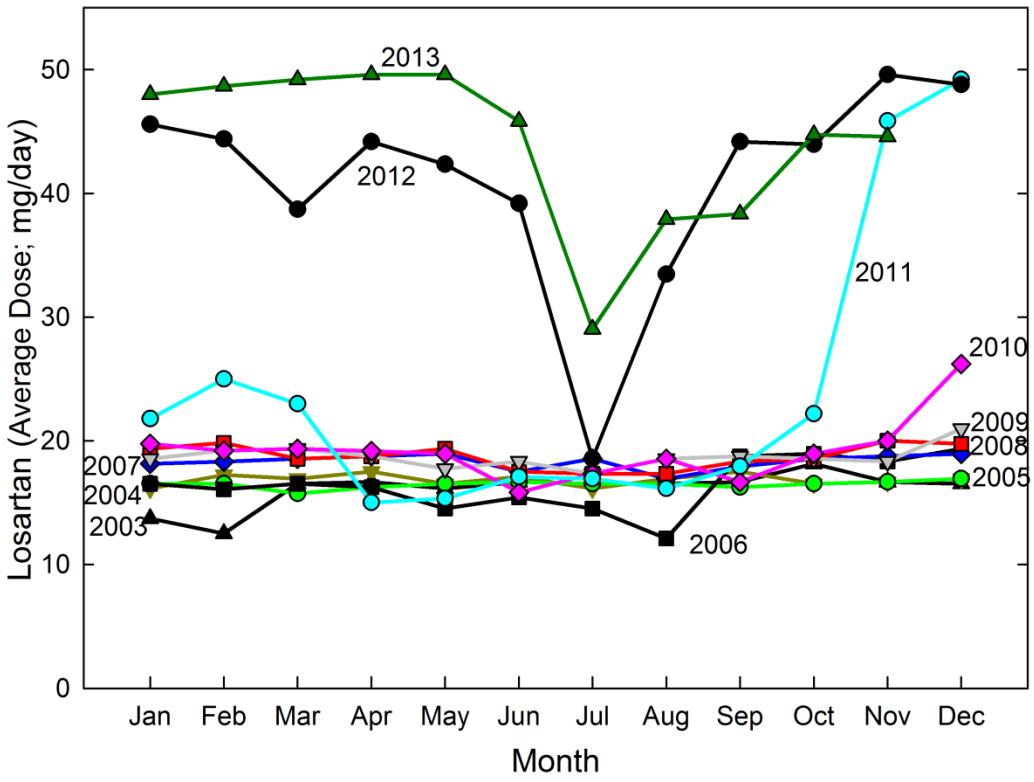

Figure 5. Monthly losartan requirements for an eleven year period (2003-2013), showing greatly decreased requirements in the summer months of years when overall dosage trends were high. 2003, black triangles; 2004, dark yellow trianges; 2005, green circles; 2006, black squares; 2007, blue diamonds; 2008, orange squares; 2009, grey triangles; 2010, red diamonds; 2011, cyan circles; 2012, black circles; 2013, green diamonds.

The detailed BP plot for 2011 is of special interest (Fig. 6). BP levels were maintained relatively constant by *decreasing* losartan dosage in the summer months and *increasing* dosage in the following winter. The sub-zero maximum daily temperatures early in the year were

associated with 25mg/day dosages. The increase in losartan requirement to 50mg/day began in the late fall when maximum temperatures were still above zero, so seeming to reflect an influence internal to the subject, as well as from the environment.

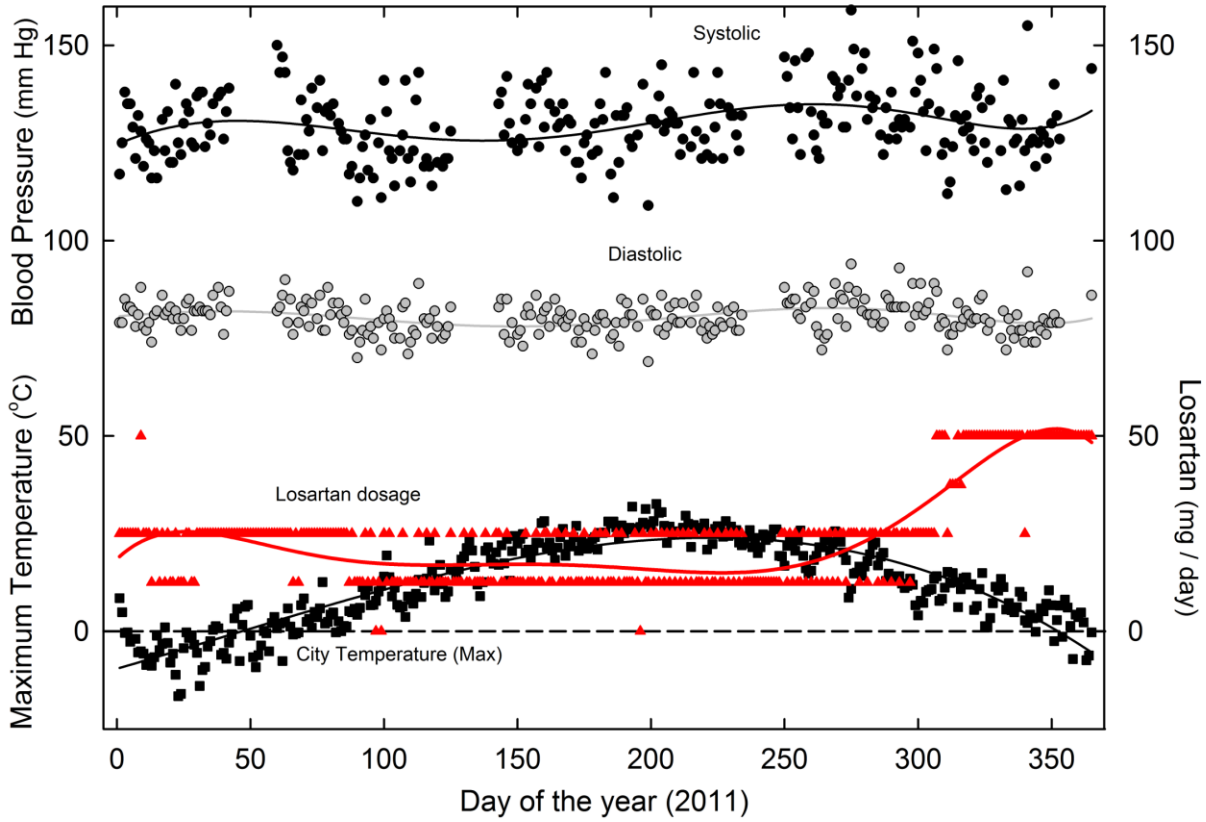

Figure 6. Daily variation in SBP and DBP in 2011, as related to (i) maximum daily environmental temperatures and (ii) varying losartan dosage. For details see Figures 1 and 3.

Plots of the same parameters as a function of daily temperature (Fig. 7), show a biphasic linear regression fit to losartan dosage. The ascending limb of the regression reflects the dosage increase from 25 mg/day in the cold early part of the year, to 50 mg/day in the less cold late part of the year. The descending limb of the regression reflects the decreasing requirement during the summer months.

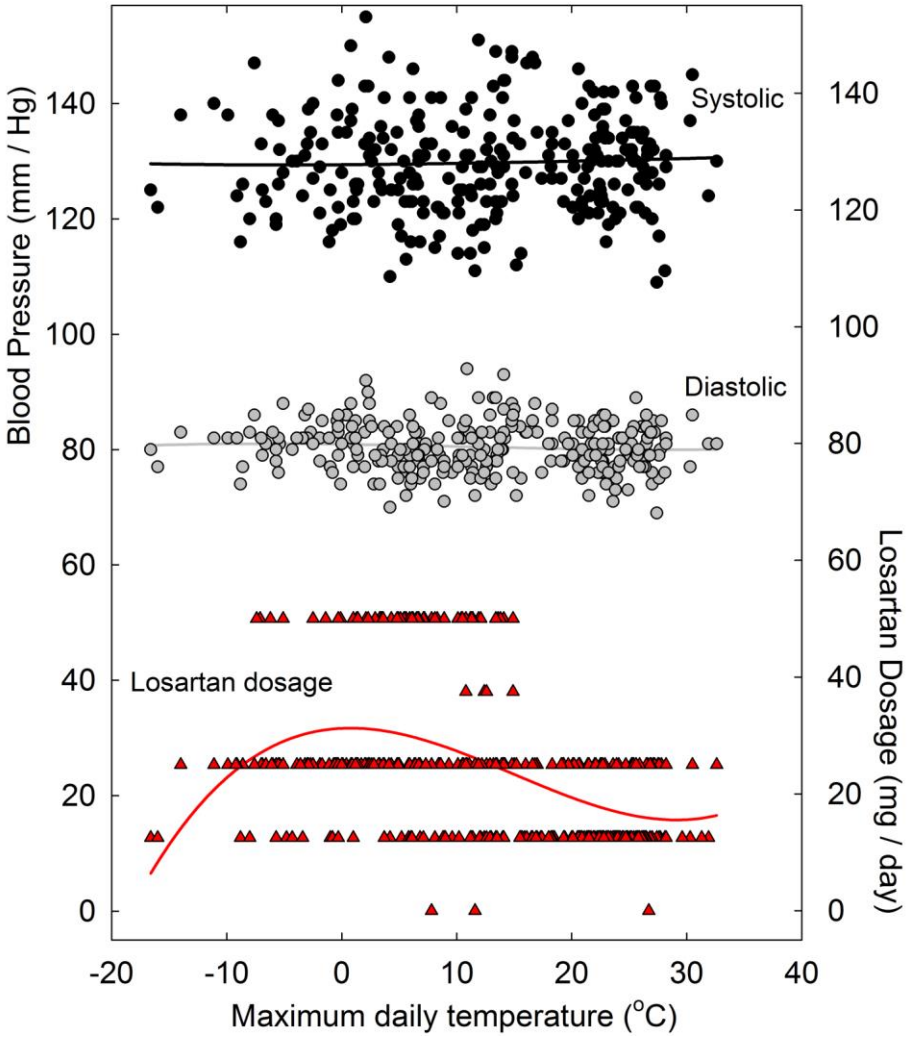

Figure 7. Daily values for SBP, DBP, and losartan dosages for the year 2011, as a function of the corresponding maximum environmental temperatures. Least-squares regression fits (third order polynomial) to the points are shown as continuous lines. This is a replot of the data of Figure 6.

Figure 8 shows similar regression plots of losartan requirement against environmental temperature for the entire eleven year period. With the exception of 2006 (mentioned above), the

curves were essentially horizontal for the 2003-2009 period. Thus, the requirement was independent of temperature. In 2010 came the first indication of the extreme seasonal influence, which was quite explicit for the years 2012 and 2013. Indeed, by extrapolation, under these conditions losartan could have been abandoned had maximum daily temperatures reached 34°C. As noted above, the curve for 2011 is anomalous since its left ascending limb reflects the increase in losartan requirement as winter approached later in the year.

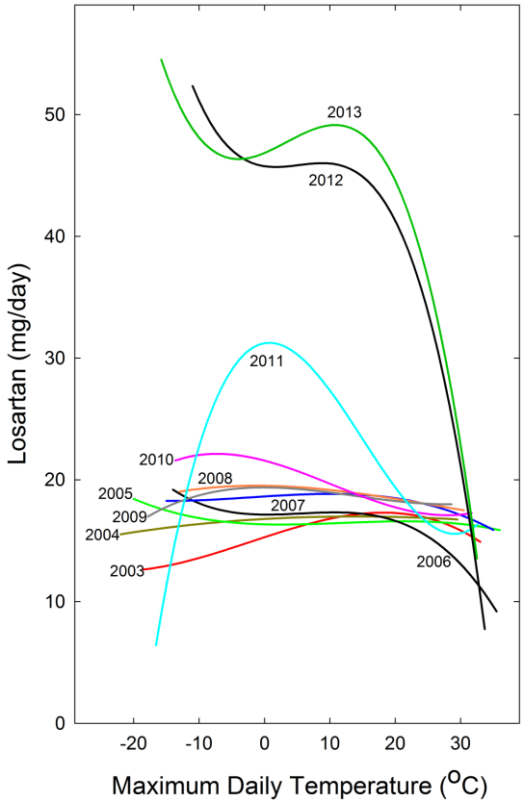

Figure 8. Yearly losartan requirements for the 2003-2013 period, as a function of daily maximum environmental temperatures throughout each year. The third order regressions (as in Figure 7), are shown for each year. Line coloring for different years follows that of the symbols shown in Figure 5.

Review

While confirming the normal small summertime decline in daily BP readings,[1-5] this case study documents a profound summertime dosage-dependent sensitivity to the BP-lowering effect of losartan. That this may also apply to other antihypertensive medications was suggested by Handler in a case study involving an ACE inhibitor.[10] Indeed, albeit controversial (see below) and not documented on an individual basis, the practice of decreasing medication in summer and increasing in winter, is widely followed.[11] Unaware of this, the present study arose from the belief that an interference with physiological homeostatic controls, which was deemed necessary for management of primary hypertension, would require close BP assessment – an assessment which would be facilitated by the digital devices that had become available for home-monitoring. Whether it is the actual BP level, or variation in that level, that is most responsible for adverse clinical consequences, is much debated.[12,13] Here, the day-to-day adjustment of losartan dosage to observed *daily* BP levels would seem to address both factors. However, the possibility that night-time BP readings might *not* be affected in a similar manner,[14,15] was not addressed.

Night-Time Dipping

ABP recordings often reveal a small dip in BP values when subjects are resting at night. Although carried out on biased groups (members of different summer and winter populations that had been referred to hypertension clinics), ABP studies in Italy[16,17] found that, in summertime, night-time dipping was less evident and SBPs were slightly *increased*; it was only with day-time BP measurements that the summertime decrease was evident. The night-time SBP increase was particularly apparent in elderly subjects receiving antihypertensive medication (type not specified). While noting that "milder sleep problems associated with hot weather cannot be

completely excluded,"[16] and that there may be "different sleeping behaviors between summer and winter,"[17] the authors suggested that there is often a, clinic-directed or self-directed, reduction in medication in summertime, either because of a measured daytime lowering of BP, or because it is "common knowledge" that such lowering would have occurred.[17] Thus, those who would reduce the number of medications, or reduce dosages (as in the present study), were cautioned by Modesti et al.[16] that "the results of our study clearly indicate that the practice of reducing treatment in the summer in the elderly based on low clinic BP values is not good, because it might be responsible for a potentially dangerous increase in night BP."

It is recognized that "patients are exposed to antihypertensive treatment for decades; yet, long-term safety of these drugs is not well-reported. Most prospective randomised trials end after a few years without long-term follow up."[18] Indeed, in a recent study Modesti et al.[3] declared that some of the limitations of their approach "would be addressed in future studies based on repeated measurements according to a longitudinal design and focusing on the assessment of temperature and BP changes within a single individual." This need for long-term single-individual studies was echoed by Cuspidi et al.,[15] and by Tomlinson et al.,[7] who called for "carefully designed studies using individual level patient data to examine this issue in more depth." To some extent, the present approach meets this requirement, but regrettably with the absence of night readings. Nevertheless, given that hypertension-related adverse cardiovascular events are less in summer, then correcting, at this time of the year, for the daytime *decrease* in SBP, may be more important that correcting for a night-time *increase*. Determining the swings and roundabouts of this is a matter for future study, but a prudent interim measure might be to take some or all of whatever medications are deemed necessary in hot weather, late in the

evening. Such a season-tailored 'chronotherapeutic approach'[15,19] touches on the issue of the period of bioavailability of a medication after ingestion, as is considered below.

Mechanism of Summer Losartan Hypersensitivity

Why is there seasonal hypersensitivity to the BP-lowering effect of losartan, and why is this effect so dosage dependent? General dosage-dependent losartan effects were evident in early short-term studies with both normal volunteers and patients.[20] Thus, Gottlieb et al.[21] noted in 1993 that the vascular dilation and BP-lowering effects were maximal with 25 mg/day and *declined* at higher doses, whereas effects deemed "neurohormonal," such as increased levels of renin and of the circulating angiotensin II octapeptide (Ang II), continued to increase at higher concentrations. With the present subject, summer losartan hypersensitivity became most evident when dosage increased from around 25mg/day to 50mg/day (Figs. 5, 8), suggesting a neurohormonal influence.

Cell surface Ang II receptors (subtypes AT_1R and AT_2R) are present in various mammalian species. It is the reaction of Ang II with AT_1R, the dominant receptor, that is blocked with high specificity by losartan.[22] Independently of losartan, the reaction triggers G_q-protein signalling that mobilises intracellular Ca^{++}, resulting in increased vascular tone. Such signalling is itself susceptible to modulation by regulatory factors – such as Regulator of G-Protein Signaling-2[9] – which are themselves subject to regulatory inputs. So determining how seasonal factors feed into this system, and whether the key seasonal factor is, indeed, temperature,[3,22] is unlikely to be easy. Although bound to plasma albumin, losartan itself is rapidly degraded to a longer-lived, pharmacologically more potent, carboxylic acid derivative, also bound to albumin; this sustains AT_1R blockade non-competitively for many hours.[21,23-25]

Thus, provided a sufficient dose is employed, and the period between doses is not too long, successive losartan doses may act cumulatively. This is consistent with the observation that, in the *spring* of 2000, BP values fell progressively, and rose progressively, each over several days, following the implementation, and then cessation, of losartan therapy. However, when losartan was restarted in the *summer* of 2002, the fall was immediate (Fig. 1). This hinted at the additional seasonal influence, *conditional* on losartan dosage, that would be uncovered ("unmasked") in future years (Figs. 4, 5, 8).

Treatment with ACE inhibitors *lowers* the circulating concentration of Ang II, so decreasing its reaction with the dominant AT_1R subtype, and thus lowering BP. However, the *increase* in the circulating concentration of Ang II, following blockage of the AT_1R subtype with losartan, should suffice to affect the losartan-insensitive, low abundance, AT_2R subtype. Activation of AT_2R usually *counteracts* the effects of AT_1R activation (e.g. vasodilation not vasoconstriction).[26,27] It is reported for hypertension-prone rats that Ang II will cause AT_2R-mediated vasodilation, *provided* AT_1R is blocked and AT_2R expression is upregulated.[28,29] Thus, activation of AT_2R is *conditional*, and is described as being "unmasked" or "trumped" when AT_1R-mediated effects are inhibited by agents such as losartan.[30,31,32] Indeed, Abdulla and Johns[33] recently reported for rats that losartan increased the fall in BP following the AT_2R receptor-associated inhibition of renal sympathetic nerve activity, which was part of the homeostatic response to total body fluid volume expansion, such as normally occurs in humans in summertime.[34] They concluded that: "The basal level of central AT_2 receptor activation is not involved in the normal renal sympatho-inhibition due to volume expansion, unless the counter-regulatory AT_1 receptors are blocked." Thus, there is again an "unmasking" effect of losartan.

While much of our knowledge currently derives from experiments with rodent strains which exhibit spontaneous hypertension, a working hypothesis consistent with the rodent data would be that in humans the AT_2R subtype comes into operation in hot weather to fine-tune the AT_1R-mediated vasoconstriction necessary to sustain BP when superficial veins dilate to enhance body cooling. This AT_2R activity might be sufficient to explain the normal small summertime BP dip found in untreated human subjects (Fig. 2). Under this condition, the excess of Ang II resulting from high losartan dosage, would be expected to react with the AT_2R, so greatly enhancing the losartan-induced fall in BP (Figs. 4, 5, 8). To this extent, the present human study is supportive of most rodent studies, and this might encourage the development of AT_2R agonists, including truncated Ang II fragments, as possible novel antihypertensive agents.[31]

Seasonal Medication Hypersensitivity

Seasonal influences on responses to specific antihypertensive medications are not well documented. Apart from logistic considerations (e.g. patient confidentiality), this may be due the relative newness of some medications, so that long-term studies are not yet available. In Japan, Hozawa et al.[1] relied on the home BP measurements of volunteers, but had no information on medications. In their longitudinal study on individual subjects, Aubinière-Robb et al.[4] relied on clinic measurements of treated hypertensive subjects, but had "incomplete prescribing data." Furthermore, being based in Scotland, their study was more concerned with the detrimental effects of increases in BP in cold weather, than of decreases in BP in hot weather. The subtropical island of Taiwan has temperatures closer to those in summer-time Ontario, but the winter-summer variation is much less. For Taiwan, Tu et al.[5] reported no influence of season on the response to antihypertensive medication, but type and dosage were unspecified.

The most definitive study to date is that of Lewington et al.[2] who related seasonal temperature changes from ten climatically diverse regions of China to the daily clinic BP measurements of 500,000 volunteers. The *percentage* differences between summer and winter did not differ between those on antihypertensive medication (type unspecified) and those who were not. However, *absolute* differences were greater in hypertensive subjects (differences averaging 11.0 mm Hg versus 9.6 mm Hg). While citing Modesti et al.[16] (see above), and while noting that the seasonal difference might make it more difficult to diagnose marginal hypertension in summertime, Lewington et al.[2] suggested that, for diagnosed hypertensive subjects, "higher doses or additional drug(s) may be required in winter to achieve the same blood pressure control as at other times of the year." In other words, contradicting Modesti et al.,[16] they advised lowering dosage in summertime. Floras[13] has recently cautioned that when marginal hypertension is diagnosed in summer-time, the resulting dosage of therapy may be suboptimum. However, in view of the seasonal medication-hypersensitivity described here, in summer months it would seem wise to begin with dosages deemed suboptimum.

Individuals with hypertension can be assorted into subpopulations.[35] Aubinière-Robb et al.[4] were able to classify their subjects into those whose BPs either did, or did not, show the small summer decline. The studies of Lewington et al.[2] suggest that this might partly be explained if members of the decliners group had lean physiques (low BMI). Since the present subject was in the summer decliner group (Fig. 2), there is here a correlation between BP sensitivity to season and seasonal BP hypersensitivity to medication (Fig. 4). Of course, further studies with other subjects are needed to establish the generality of this correlation.

The J Curve

While the benefits of decreasing blood pressure are recognized, there comes a point below which there are negative consequences (e.g. AKI). This is referred to as the "J curve" phenomenon and focuses attention on the inflection points where low SBP and DBP values become hazardous.[36] The present study suggests that the inflection point could vary on a seasonal basis.

Greater awareness of seasonal factors may serve to emphasize more widely the need for close self-monitoring of BP. Furthermore, although randomized, double-blind, trials, may result in recommendations for increases in losartan dosages (e.g. Konstam et al.[37] advise elevation from 50 mg to 150 mg), it would seem the climate of the country where such trials have taken place should be taken into account when assessing the risk-benefits of such regimens. Finally, as noted by Verberk et al.,[14] there is the obvious point that there may be direct economic benefits to health care systems if excessive dosages of costly medications are avoided.

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"Two roads that diverged" having reconverged, this paper is dedicated to W. Stanley Peart and James F. Mowbray, whose inspiring mentorship guided me to the road "less travelled by."

Disclosures

None.

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