Summertime dosage-dependent hypersensitivity to an angiotensin II receptor blocker

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Running title: Seasonal dosage-dependent hypersensitivity to losartan

ABSTRACT

Summertime dips in blood pressure (BP), both in normotensive and hypertensive subjects, are well known. However, the dips are small and are not related to particular forms or doses of antihypertensive medication. Nevertheless it is the practice in some quarters to decrease antihypertensive medication in summer, and/or increase in winter. Large scale studies being inconclusive, there are calls for long-term examination of the relationship between environmental temperature and blood pressure in single individuals under medication. While analyzing data from a subject whose BP had been controlled for a decade with the angiotensin-II receptor blocker losartan, an extreme, dosage-dependent, summertime dip came to light. Downward dosage adjustment appeared essential and may have prevent hypotension-related pathology. The benefits of aggressive medication (the "J curve" phenomenon) being debated, the possibility of seasonal hypersensitivity, explicable in terms of differential signaling by countervailing receptors, should be taken into account when considering dosage adjustments in hypertensive subjects.

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INTRODUCTION

Small summertime declines in blood pressure (e.g. 5-10 mm Hg) have long been known, both in normotensive and hypertensive subjects. Nevertheless, perhaps because adverse cardiovascular events are more frequent in winter, it is the practice in some quarters to decrease antihypertensive medication in summer, and/or increase in winter (Charach, Rabinovich & Weintraub, 2004). However, this is controversial. Ambulatory blood pressure (ABP) recordings often reveal a small dip in BP values when subjects are resting at night (Fedecostante et al., 2012). In Italy, Modesti et al. (2006) reported that in summer this night-time dipping was less evident, and systolic values (SBPs) were slightly *increased*; it was only with day-time BP measurements that the summer decrease was evident. They cautioned 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.' On the other hand, based on clinic BP measurements of 500,000 subjects drawn from ten climatically diverse regions of China, Lewington et al. (2012) recently affirmed that '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.' Indeed, Modesti (2013) has acknowledged that 'it is possible that heat-exposed subjects need lower dosages … because of lower BP in warm conditions.'

Despite many such studies, seasonal variations in BP have not been clearly related to particular forms or dosages of medication in individual subjects. Handler (2011) reported a case in California where the subject, based on home BP readings and postural hypotension, had opted to stop medication in summer, but there were few details. Furthermore, seasonal variations in BP have not been related to the controversial so-called "J curve" phenomenon (Mancia & Grassi,

2014; Fuchs & Fuchs, 2014). While the benefits of decreasing BP are clear, there comes a point below which there are negative consequences, marked by an inflection on plots of adverse cardiovascular events against BP. Such consequences include acute kidney injury (AKI), cases of which are becoming increasingly evident (Tomlinson et al., 2013). While analyzing data from a subject whose BP had been controlled for over a decade with losartan, an angiotensin II receptor blocker (ARB), an extreme, potentially dangerous, dosage-dependent, summer-time influence came to light. Given that this ARB is now a treatment of choice for many millions of hypertensive subjects it is unlikely that this is an isolated case.

METHODS

Beginning in January 2000, resting BP readings were taken at least once daily (usually both in early morning and late evening) by the subject (DRF) at his home. The continuing accuracy of his Omron digital BP monitor (model HEM-712C) was ascertained by comparing with readings from his mercury sphygmomanometer, and with those obtained in his physician's office.

Since Ontario Climate Centre records of daily temperatures 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 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.

Over the 2003-2013 period, 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. Standard blood and urine tests remained within normal ranges, except that on occasions creatinine levels approached high normal. 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). No institutional review board approval was needed since the subject is the author of this paper.

RESULTS

In August 1999, mild hypertension (circa 150/90 mm Hg) was discovered during routine physical examination of a healthy 60 year old biomedical researcher. His physician prescribed the ARB, losartan (50mg/day). Postural hypotension, and an instance of acute renal colic, encouraged close home BP monitoring with dosage adjustment aiming to sustain BP values in the 130/80 mm Hg range. Our present focus being the 2003-2013 period, details of the first three years (2000-2002) may be found elsewhere (Forsdyke, 2013). In 2001, when medication was avoided, there was the expected small summertime dip in both SBP and DBP, which correlated inversely with environmental temperature (Fig. 1).

A monthly break-down of losartan requirements for the entire eleven year period is shown in Figure 2. At the doses employed between 2003 and 2009 (average 16-18 mg/day), usually no 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, for unknown reasons, a sharp increase in

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

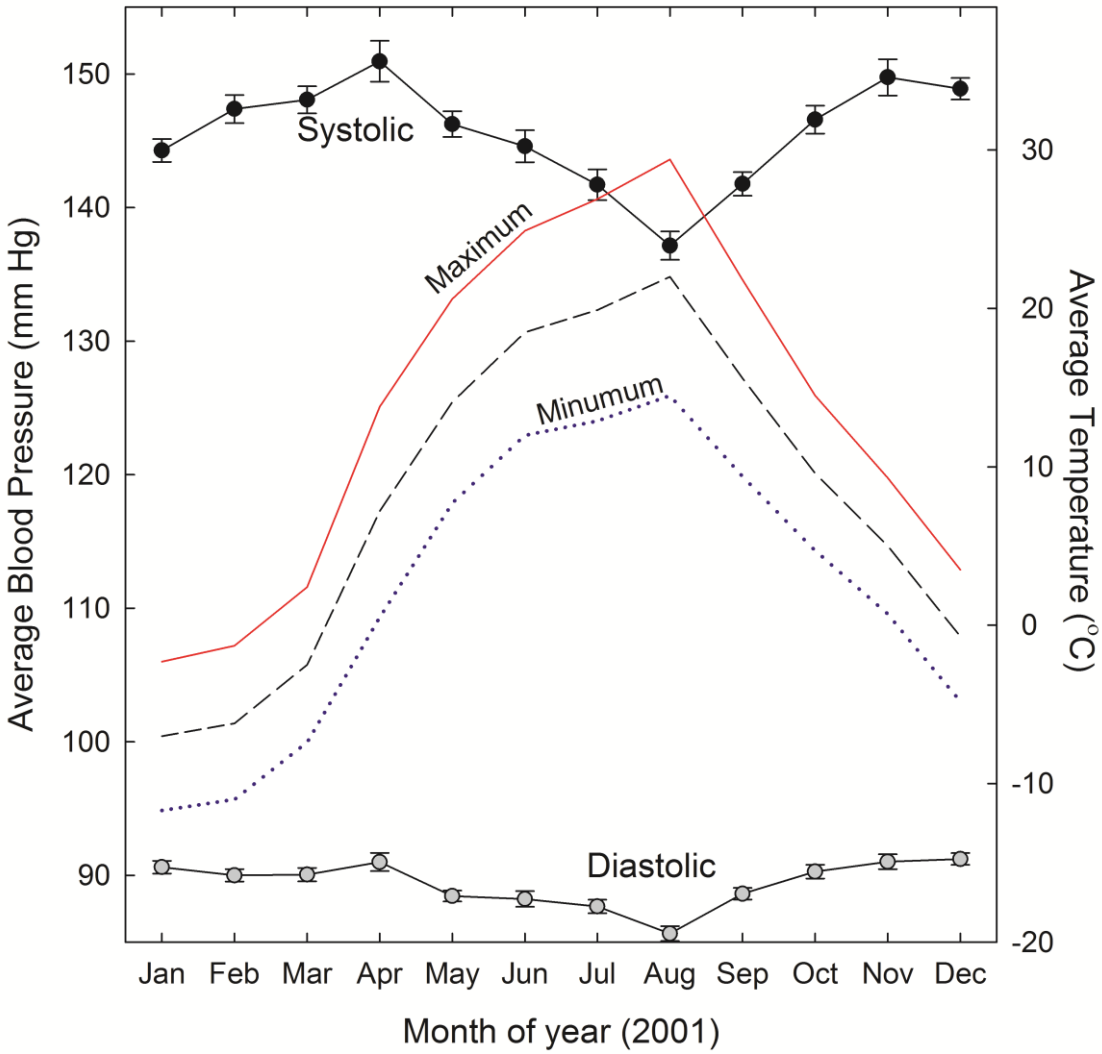

Figure 1. Seasonal variation in SBP and DBP in absence of antihypertensive medication. Daily values for each month in the year 2001 are averaged and plotted with standard errors. Corresponding monthly average temperature values are shown without symbols (*maximum*, continuous red line; *average*, dashed black line; *minimum*; dotted blue line).

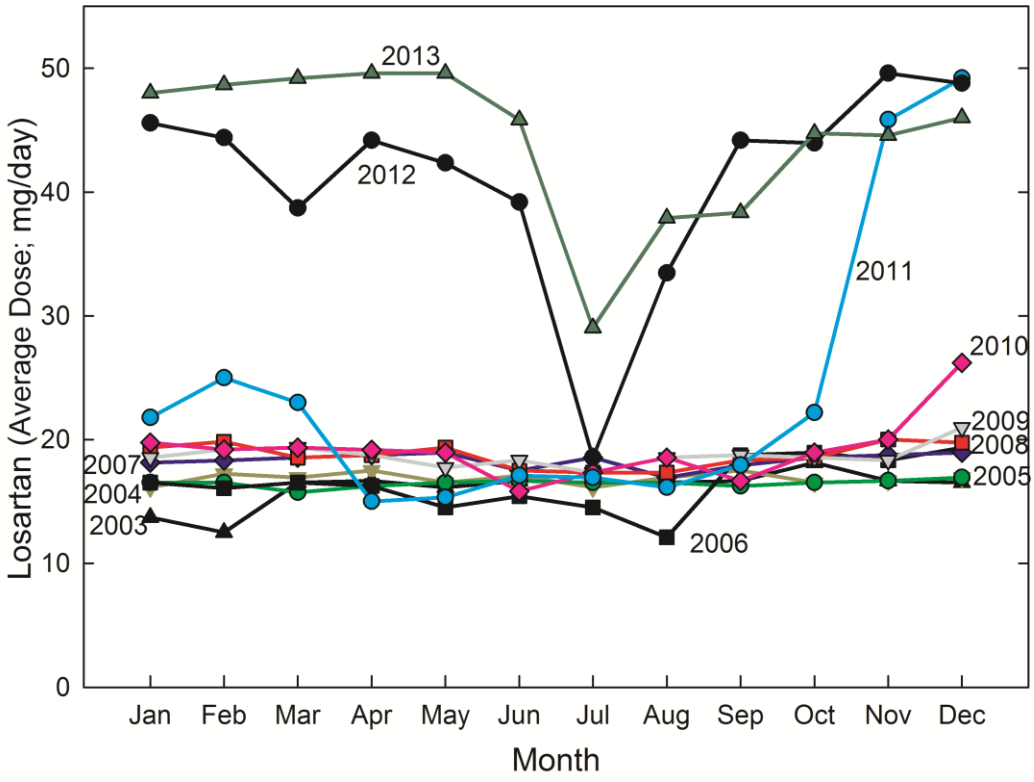

Figure 2. Monthly losartan requirements for an eleven year period (2003-2013), showing greatly decreased requirements in the summer months of years when overall dosage trends were high. 2003, black triangles; 2004, dark yellow trianges; 2005, green circles; 2006, black squares; 2007, blue diamonds; 2008, orange squares; 2009, grey triangles; 2010, red diamonds; 2011, cyan circles; 2012, black circles; 2013, green diamonds.

Figure 3 shows regression plots of daily losartan requirement against environmental temperature for the eleven year period (2003-2013). With the exception of 2006 (see above) the curves were essentially horizontal for the 2003-2009 period. Thus, the losartan requirement was independent of temperature. In 2010 came the first indication of the extreme seasonal influence,

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which was explicit for the years 2012 and 2013. Indeed, by extrapolation, under these conditions losartan could have been abandoned had maximum daily temperatures reached 35°C. The curve for 2011 is anomalous since its left ascending limb reflects an increase in losartan requirement as winter approached later in the year, but temperatures were then still above zero.

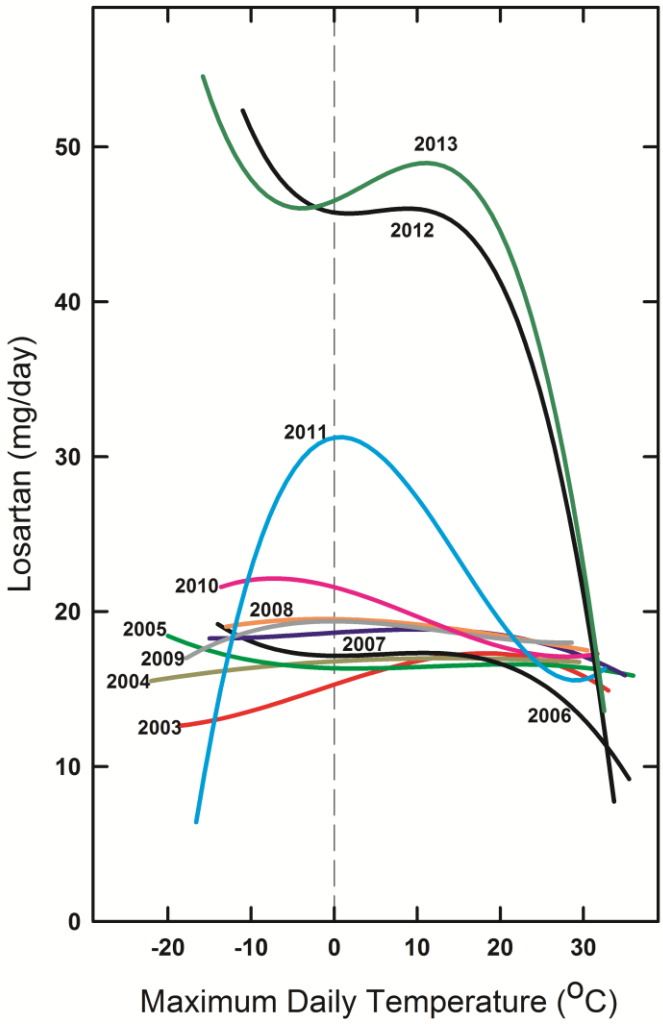

Figure 3. Losartan requirements for the 2003-2013 period as a function of daily maximum environmental temperatures throughout each year. The third order regressions through data points are shown for each year. Line colouring for different years follows that of the symbols shown in Figure 2.

DISCUSSION

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' (Messerli, Williams & Ritz, 2007). Indeed, recently Modesti et al. (2013) 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.' Likewise, Tomlinson et al. (2013) called for 'studies using individual level patient data.' To some extent, the present approach meets this requirement, but regrettably with the absence of nighttime readings. Nevertheless, given that hypertension-related adverse cardiovascular events are less in summer (Schwartz & Kloner, 2012), then correcting in summer for the daytime *decrease* in SBP, may be more important that correcting for a possible 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' touches on the issue of the period of bioavailability of a medication after ingestion, as is considered below.

General dosage-dependent losartan effects were evident in early short-term studies with both normal volunteers and patients (Christen et al., 1991). Thus, Gottlieb et al. (1993) noted 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, 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 high-affinity receptor, that is blocked with high specificity by losartan (Wong et al., 1991). The reaction normally 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 (Tang et al., 2003) – 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 (Schwartz & Kloner, 2012; Modesti et al., 2013), 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 (Munafo et al., 1992; Lo et al., 1995). Thus, provided a sufficient dose is employed, and the period between doses is not too long, successive losartan doses may act cumulatively.

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; Matsubara, 1998; Gasparo et al., 2000). 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 (Cosentino et al., 2005; Savoia et al., 2005). 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 (Li & Widdop, 2004; McCarthy et al., 2013; Schalekamp & Danser,

2013). Indeed, Abdulla and Johns (2013) 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 (Kristal-Boneh et al., 1993). 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.

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 summer BP dip in untreated human subjects (Fig. 1). 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. 2, 3). To this extent, the present human study is supportive of most rodent studies. It also suggests that the inflection points on J-curves (Mancia & Grassi, 2014; Fuchs & Fuchs, 2014) could vary on a seasonal basis. Greater awareness of seasonal factors may emphasize more widely the needs both for close self-monitoring of BP, and for more comprehensive softwares in monitoring devises that would allow recommended daily medication dosages automatically to take into account environmental temperatures and recent BP readings. Furthermore, although randomized, double-blind, trials, may result in recommendations for increases in daily losartan dosages (e.g. Konstam et al. (2009) advise elevation from 50 mg to 150 mg), it would seem the climate of the country where such trials have taken place should be considered when assessing

the risk-benefits of such regimens. Finally, as noted by Verberk et al. (2007), there may be direct economic benefits to health care systems if excessive dosages of costly medications are avoided.

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