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Mini-review

Drug-induced hypertension: Know the problem to know how to deal with it

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ABSTRACT

Arterial hypertension remains the world's leading mortality risk factor and despite overwhelming evidence that blood pressure-lowering strategies greatly reduce the cardiovascular risk, a substantial proportion of hypertensive individuals worldwide fail to achieve an optimal blood pressure control under treatment. Among the causes responsible for the gap existing between blood pressure lowering potential of the different antihypertensive treatments and real-life practice is the presence of drug-induced hypertension. Many therapeutic agents or substances may directly favour an increment of blood pressure values or counteract the blood pressure lowering effects of antihypertensive drugs. Excessive water and sodium retention, direct vasoconstriction or sympathomimetic activation are major mechanisms of action of such substances. The present manuscript will review medications and other substances that may increase blood pressure, also suggesting the choice of the more appropriate antihypertensive agents to employ when withdrawal of the substance or drug causing an elevation of blood pressure values is not possible.

1. Introduction

Hypertension represents the world's leading mortality risk factor, with an independent continuous relationship with the incidence of several cardiovascular events, including stroke, myocardial infarction, sudden death, heart failure as well as end-stage renal disease [1]. Accordingly, blood pressure (BP) reduction is paralleled by marked reductions in fatal and nonfatal outcomes in hypertensive patients [2]. Nevertheless, several observational surveys continue to show unsatisfactory BP control in the general population of hypertensive patients under treatment [3].

A major factor contributing to this therapeutic failure is represented by the use/abuse of medications and other substances that may cause a sufficient increase on BP or counteract the BP lowering effects of major antihypertensive drugs to raise the suspicion of secondary hypertension. Indeed, many therapeutic agents or chemical substances may induce a transient or persistent BP elevation, or significantly interfere with the antihypertensive agents by several mechanisms, including sodium retention and extra-cellular volume expansion, sympathetic nervous system activation, or direct vasoconstriction.

The present manuscript aimed to review the state of the art on potential causes of hypertension induced by use/abuse of drugs or substances, with a special focus on preferred antihypertensive drugs to utilize when drug-induced hypertension represents an ineluctable situation.

2. Steroids, nonsteroidal anti-inflammatory compounds (NSAIDs) and liquorice

Both mineralocorticoids and glucocorticoids may increase BP values. In details, mineralocorticoids such as fludrocortisone, utilized in clinic to treat Addison's disease, congenital adrenal hyperplasia syndrome and orthostatic hypotension in the elderly, mainly act at the level of the distal tubule of the kidney, where promote an active reabsorption of sodium and an associated passive reabsorption of water, with a concomitant active secretion of potassium. In turn, this results in an increase of BP and blood volume. Glucocorticoids such as hydrocortisone, prednisone and methylprednisolone show a lower, mineralocorticoid activity. Nevertheless, such minor affinity is enough to induce a mineralocorticoid receptor activation and increased sodium resorption, especially when these steroids are utilized at high doses [4]. While the promiscuous activation of the mineralocorticoid receptor by excess glucocorticoid certainly plays a role in the glucocorticoid-mediated hypertension, increasing evidence argues against this being the only factor. For example, the elevation of BP after administration of glucocorticoids in patients suffering from Addisonian shock occurs too

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rapidly to be explained by renal mechanisms alone and suggests the crucial role of vascular tissues in *acute* BP responses [5]. Experimental and in vitro evidence have described an upregulation in angiotensin II type I (AT I) receptors and an increased influx of Na^+ and/or Ca^{2+} into smooth muscle cells of the vascular wall induced by glucocorticoids [6,7]. Other authors have suggested the contribution of endothelial dependent pathways (i.e. a reduced NO availability) to the BP response induced by glucocorticoid administration [8]. Particularly, destabilization of the endothelial nitric oxide synthase (*eNOS*) mRNA [9] has been described in experimental and in vitro studies.

Generally, the steroids-induced hypertension is a reversible phenomenon. Discontinuation of them usually leads to normalization of BP. As the exact vascular and cardiac mechanisms accounting for the BP elevation under steroid treatment remain largely unknown, the most rationale treatment for steroids-induced hypertension is to counteract its renal effects by reducing Na and fluid retention. Thus, the diuretic is the first-choice antihypertensive agent, added to a renin-angiotensin-system blocker, i.e. an ACE-inhibitor or an angiotensin receptor blocker (ARB), to reach a better BP control, especially if low serum potassium occurs.

A large body of solid literature homogeneously documents an association between non-steroidal anti-inflammatory drugs (NSAIDs) and increased BP. NSAIDs, through the blockade of cyclooxygenase (COX)-1 and -2 activity, decreases prostaglandin synthesis, particularly PGE2 and PGI2, with vasodilation and sodium excretion properties in the kidney. This induces a reduced peripheral vasodilation together with an enhanced water and sodium retention, resulting in BP elevation. A meta-analysis of studies has shown that prolonged use of NSAIDs cause a significant increase in BP of about 5 mmHg [10]. The NSAIDs-induced hypertension is more evident in patients with chronic kidney disease, in whom hypertension is often accompanied by fluid retention, leading to peripheral oedema and heart failure [10]. Of note, NSAIDs are known also to antagonize the clinical efficacy of several antihypertensive drugs, as highlighted by observational studies. In particular, exposure to NSAIDs often require intensification of antihypertensive therapy in patients on treatment with ACE-Inhibitors or ARBs, without interfering with the efficacy of Ca-antagonists and central acting drugs [11,12]. Thus, patients requiring treatment with NSAIDs should preferentially assume antihypertensive drugs not interfering with the renin-angiotensin system.

Evidence of BP elevations with COX-2 selective inhibitors are quite similar to that observed among nonselective NSAIDs. In a dedicated meta-analysis, the authors evidenced that COX-2 selective inhibitors appear to induce greater hypertension than non-selective NSAIDs. However, this response was heterogeneous, with markedly raised BP associated with rofecoxib (which has since been withdrawn from the market) and etoricoxib, whereas celecoxib appeared to have little BP effect [13]. In such scenario, acetaminophen has been regarded for a long time as a safe treatment option. In a randomized, double-blind, placebo-controlled, crossover study it was documented that acetaminophen intake (1 g TID) on top of standard cardiovascular therapy for 2 weeks was associated with a significant increase in mean systolic and diastolic BP in patients with coronary artery disease [14]. Again, it was observed that acetaminophen may interfere with the antihypertensive efficacy of ramipril, valsartan or aliskiren. Thus, cautions is necessary when this compound is taken chronically in patients under treatment with RAS blockers [15]. The mechanism responsible is not fully clear, but it seems to involve the inhibition of COX-2 receptors [16] and/or an activation of cannabinoid receptors [17].

Among non-therapeutic substances, chronic excessive liquorice consumption increases the BP through its main active ingredient, the glycyrrhizic acid, which inhibits 11-beta-hydroxy-steroid dehydrogenase. This enzyme converts cortisol to cortisone, producing an excess of mineralocorticoid activity. A recent meta-analysis documented that chronic consistent ingestion of liquorice or other products containing glycyrrhizic acid induces a state of pseudohyperaldosteronism, characterized by an increase of both systolic and diastolic BP, together with a suppression of plasma potassium, renin and aldosterone [18].

3. Recombinant human erythropoietin

Erythropoietin is a hypoxia-induced hormone that is essential for normal erythropoiesis. Recombinant Human Erythropoietin (rHuEPO) is a useful compound to correct anemia secondary to malignancies or end-stage renal failure. Hypertension develops in about 20–30% of patients receiving r-HuEPO [19], usually 2 weeks to 4 months after initiation of treatment. In a cohort of pre-dialysis patients it was demonstrated that chronic treatment with r-HuEPO induced a significant increment of BP values [20], an effect confirmed in acute conditions in hemodialysis patients [21]. Suggested mechanisms include an increased blood viscosity, activation of the local RAS system, increased ET-1 production, decreased NO synthesis, and increased vasoconstriction [22]. Management of hypertension-related EPO administration requires up titration of current antihypertensives, increasing when possible the time interval between EPO doses, or adding diuretic therapy.

4. Oral contraceptive pills

Oral contraceptives may induce hypertension in approximately 5–10% of women utilizing first-generation high dose estrogen contraceptives [23]. More recent evidence indicated that even the lower-dose combination pills containing 20 μg of estrogen may significantly raise BP values [24]. A meta-analysis conducted in 270,284 participants showed a positive association between duration of oral contraceptive use and risk of hypertension, with the risk of hypertension increased by 13% for every 5-year increment in oral contraceptive use [25]. Other parameters able to increase susceptibility to develop hypertension include family history of hypertension, pre-existing pregnancy-induced hypertension, obesity, age older 35 years.

The phenomenon is reversible, with a return of BP to pre-treatment levels usually within 3 months of discontinuing oral contraceptives [26]. In a more recent prospective trial, it was documented that the combined hormonal contraceptive vaginal ring releasing 15-mcg ethinylestradiol and 120 μg of etonogestrel daily was associated with a significant increase of 24-h diastolic BP [27]. The mechanism responsible involves an increased angiotensin synthesis in the liver, leading to an enhanced angiotensin II generation and aldosterone secretion, ultimately causing sodium resorption and water retention [28]. No significant increase in BP values was seen in progestin-only pills users [29] or among postmenopausal women taking oral and transdermal hormone replacement therapy [30,31].

5. Alcohol, caffeine, psychostimulant drugs and nasal decongestants

Excessive alcohol intake has been shown to increase BP values and reduce the efficacy of antihypertensive therapy. A prospective cohort study conducted in middle-aged men analyzed the relationship of alcohol consumption to baseline BP and average annual BP change. A multivariate analysis demonstrated that the baseline systolic BP was 3.9 and 5.0 mmHg higher in drinkers consuming 200–299 and > 300 g alcohol/week, respectively, compared with non-drinkers, with a greater annual BP increase. Baseline diastolic BP was significantly associated with alcohol consumption, but annual BP change was not [32]. A recent Mendelian randomization study suggested that the relationship between alcohol intake and risk of arterial hypertension might be causal [33].

It is documented that caffeine can increase BP through an increased sympathetic activity and catecholamine release, as well as acting as antagonist of endogenous adenosine, a recognised coronary vasodilator [34]. In the first hour of ingestion, 200–300 mg of caffeine may lead to

an increased systolic and diastolic BP of 8.1 and 5.7 mmHg, respectively. The acute BP response to caffeine disappears after 2 weeks, suggesting a tolerance to BP elevations among habitual caffeine consumers [35]. Thus, caffeine is a component in coffee that may influence BP in acute but not in chronic conditions [36].

Several so-called recreational drugs can cause acute or chronic increase of BP. Among others, cocaine is one of the most important and used. Given the different topic of this review, the BP response to this drug will not be considered.

Nasal decongestants, such as phenylephrine, pseudoephedrine and naphazoline hydrochloride, are commonly used to treat symptoms of rhinitis and rhinorrea. They activate the sympathomimetic nervous system by stimulating the alpha-1 adrenergic receptors on vascular smooth muscle causing vasoconstriction. In a meta-analysis conducted in twenty-four trials in adults, pseudoephedrine caused a small but significant increase in systolic BP and heart rate, with no effect on diastolic BP [37].

6. Antiangiogenic cancer therapies

Physiologically, VEGFs (vascular endothelial growth factors) and their receptors play a critical role in vascular angiogenesis, also controlling endothelial function, and vascular tone. Unfortunately, VEGF signaling actively contributes to the angiogenesis that promotes the growth and metastatic spreading of tumors. For these reasons, VEGF inhibitors represent a modern and valuable strategy in the management of a number of malignancies, yielding improved survival outcomes. Common VEFG inhibitors include bevacizumab, lapatinib, sunitinib, and sorafenib. However, they may also lead to clinically relevant toxicities, especially hypertension. In a randomized, controlled, open-label, phase 3 trial conducted in patients with malignant pleural mesothelioma, addition of bevacizumab to the standard care led to the development of severe hypertension in 23% of patients [38]. The hypertensive effect disappears upon drug withdrawal [39].

Sorafenib, commonly utilized in kidney and hepatic carcinoma, has been shown to increase systolic and diastolic BP, an effect already evident in the first 24 h after administration [40]. The BP rising effects of sorafenib were confirmed by a large meta-analysis, showing that the administration of this drug was associated with an incidence of hypertension in 23.4% of patients and severe hypertension in 5.7% of patients [41].

The elevation of BP related to the use of VEGF-inhibitors is strictly connected with the mechanism of action of these medications, which include a decreased nitric oxide and prostacyclin production, as well as stimulation of endothelin-1 receptors. These alterations promote vasoconstriction that, combined with capillary rarefaction due to the antiangiogenetic effect of the drug, induces a significant increase of peripheral vascular resistances [42]. Accordingly, hypertension should be considered as a class effect. Globally, incidence of hypertension is dose-dependent, with a higher incidence in pre-existing hypertension, elderly and/or overweight subjects.

The optimal management of this form of hypertension is, at present, not clear. When treatment with VEGF inhibitors is planned, patients should be checked for the presence of cardiovascular comorbidities and risk factors. BP values should be checked weekly, in order to maintain BP within the values of 130/80 mmHg. Withdrawal or dose-reduction of antiangiogenic medication should be considered in the presence of hypertensive emergencies/urgency or if the introduction of antihypertensive drugs is not sufficient to control BP. As the majority of the pro-hypertensive effects of these medications relies on their capacity to increase peripheral vascular resistances, dihydropyridine type calcium channel blockers and RAS inhibitors may be considered the most appropriate classes of anti-hypertensive dugs in these subjects [42,43].

7. Immunosuppressive medications

Development or deterioration of hypertension is quite common among those patients receiving the immunosuppressive calcineurin inhibitor cyclosporine. Several studies investigating this issue in renal transplanted patients reported incidence of hypertension associated to cyclosporine ranging from 32% to 81% [44,45], reaching the frequency of about 100% in cardiac transplant recipients [46]. Cyclosporine-induced hypertension is often observed also in patients with autoimmune disease [46]. The Cochrane Central Register of Controlled Trials selected available double-blind, randomized, controlled trials comparing cyclosporine to placebo. The results demonstrate a highly statistically significant increase in BP associated with cyclosporine according to a dose-related effect, with lower doses (1–4 mg/kg/d) increasing mean BP by an average of 5 mmHg and higher doses (> 10 mg/kg/d) increasing mean BP by 11 mmHg on average [47].

Mechanisms accounting for cyclosporine-induced hypertension include systemic and renal vasoconstriction and nephrotoxic effects. In details, cyclosporine is able to induce a systemic and renal sympathetic nervous system stimulation, resulting in a greater sodium reabsorption at the level of renal proximal tubule. The drug also induces a renal and systemic vasoconstriction due to an over-production of endothelin-1 in larger pre-glomerular arteries by activation of the endothelin-A receptors. A reduced synthesis of vasodilator prostaglandins is also observed in cyclosporine-treated patients, together with a reduced activity of endothelial-derived nitric oxide [48]. Potential mechanisms of cyclosporine-induced hypertension and nephrotoxicity are tentatively summarized in Fig. 1. Given the evidence that virtually the totality of patients receiving cyclosporine develops hypertension, and the crucial importance of maintaining an appropriate level of immunosuppression in these patients, the choice of the appropriate antihypertensive drug, if any, is a crucial issue, especially in terms of graft/patient survival. Nevertheless, a detailed assessment of different antihypertensive compounds on this aspect has not been, at present, investigated.

In the present issue of the *Vascular Pharmacology*, Marienhagen et al. [49] shows results from a retrospective study assessing the survival and risk of graft failure in kidney transplant patients with pre-existing and post-transplant hypertension receiving different classes of antihypertensive medications. The authors found a significant relationship between increasing cyclosporine dose/serum concentration, greater systolic BP values and lower glomerular filtration rate, with post-

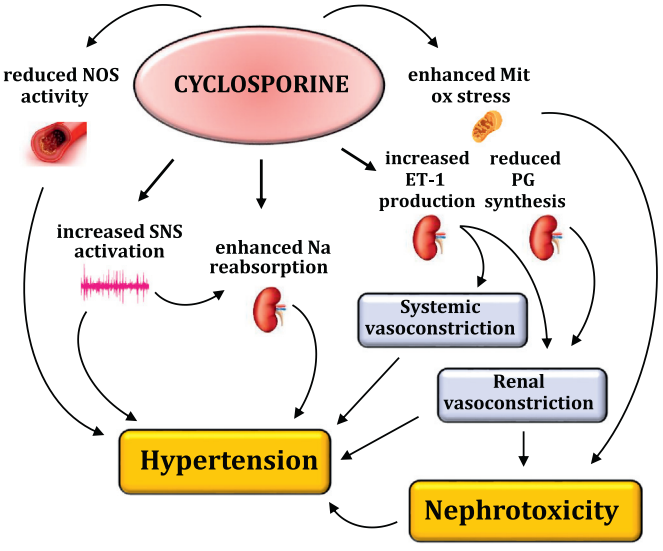

Fig. 1. Proposed mechanisms whereby cyclosporine induces hypertension and nephrotoxicity. NOS: nitric oxide synthase; Mit: mitochondrial; ET-1: endothelin-1; PG: prostaglandin; SNS: sympathetic nervous system; Na: sodium.

transplant hypertension representing an independent major risk factor for graft/patient survival. Of note, all antihypertensive treatments were able to reduce effectively systolic BP. However, the risk of graft failure/death was significantly increased when hypertension was treated with ACE inhibitors or β-blockers, but not with ARBs and/or Ca-channel blockers. Any other immunosuppressive drug utilized in combination with cyclosporine, including prednisolone, mycophenolic acid, azathioprine and/or sirolimus failed to affect patient and/or graft survival.

The main conclusion of this study is that graft/patient survival is influenced by the class of antihypertensive medication, suggesting ARBs and Ca-antagonists as the most safety option to treat cyclosporin-induced hypertension.

Although future reports preferentially with a prospective randomized design should confirm the findings of this paper, the results presented by Marienhangen et al. deserve additional comments. The impact of ACE-inhibitors emerging in the present study is in line with those reported by the Cochrane Database of Systematic Reviews, in which in ACE inhibitors resulted to be detrimental in the management of hypertension in kidney recipients [50]. Such result is not surprising and in keeping with the renal hemodynamic changes induced by cyclosporine. Indeed, in experimental conditions, administration of cyclosporine results in an acute fall in renal blood flow and a rise in renal vascular resistance. Acutely administrated, captopril does not prevent cyclosporine-induced renal vasoconstriction, thus excluding that this effect might be mediated by angiotensin II [51]. These considerations, however, do not justify the favourable role played by ARBs. Unfortunately, the study design by Marienhagen et al. [49] does not allow a mechanistic clarification.

The second comment deals with the impact of Ca-antagonists on graft survival. As above described, most of the cyclosporine-mediated vascular effect involve an excessive endothelin-1 together with a reduced nitric oxide activity. These known mechanisms totally fit with those protective properties by Ca-antagonists toward vasculature. Indeed, Ca-antagonists inhibit the effects of endothelin-1 at the level of vascular smooth muscle cells by reducing Ca^{2+} inflow and facilitating the vasodilator effects of NO. The resistance circulation is particularly dependent on extracellular Ca^{2+}, thereby explaining why Ca-antagonists effectively inhibit ET-induced vasoconstriction in vitro and in vivo [52]. In addition, Ca-antagonists demonstrated a dramatic vascular antioxidant activity, which likely protects from atherosclerosis [53]. In such scenario, recent evidence highlighted that oxidative stress plays an important role in cyclosporine-induced nephrotoxicity. In particular, cyclosporine is able to increase mitochondrial reactive oxygen species production. In turn, this modifies the redox balance, causes lipid peroxidation and thereby induces nephrotoxicity (Fig. 1) [54]. Of course, the possibility that cyclosporine-mediated oxidant excess involves systemic vasculature awaits future clarification.

Tacrolimus is another immunosuppressive agent that inhibits calcineurin clinically utilized for prophylaxis of organ rejection. Similar to cyclosporin, tacrolimus has also been associated with development/worsening of hypertension. The pro-hypertensive effects of tacrolimus, however, seem to be significantly inferior than with cyclosporine [55]. Therefore, a switch to tacrolimus may be considered in patients who develop a form of cyclosporine-associated hypertension resistant to antihypertensive treatment.

8. Conclusions

Many therapeutic/recreational substances can induce a persistent or transient increase in BP or interfere with the effect of antihypertensive drugs, representing an important cause of secondary hypertension, often unappreciated or undervalued. A careful medical history is a fundamental tool whereby the physician may obtain information about a possible drug-induced hypertension. In particular, main aspects that need to be investigated include life habits, consumption of alcohol, anti-inflammatory or analgesic drug intake, even for transdermal administration in the form of creams, ointments, lotions for dermatological use. Generally, the deleterious impact of such substances is greater in the elderly and in patients who have pre-existing hypertension or chronic renal failure. A specific attention must be paid to the possible use of recreational drugs, especially in the presence of a sudden and unexplained rise in BP in young subjects.

Once drug-induced hypertension is identified, the withdrawal of the drug is recommended. When this is not possible, the choice of specific antihypertensive drugs utilized at full doses and their appropriate combination usually lead to a satisfactory BP control.

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