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Drug induced hypertension – An unappreciated cause of secondary hypertension

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ABSTRACT

Most patients with hypertension have essential hypertension or well-known forms of secondary hypertension, such as renal disease, renal artery stenosis, or common endocrine diseases (hyperaldosteronism or pheochromocytoma). Physicians are less aware of drug induced hypertension. A variety of therapeutic agents or chemical substances may increase blood pressure. When a patient with well controlled hypertension is presented with acute blood pressure elevation, use of drug or chemical substance which increases blood pressure should be suspected. Drug-induced blood pressure increases are usually minor and short-lived, although rare hypertensive emergencies associated with use of certain drugs have been reported. Careful evaluation of prescription and non-prescription medications is crucial in the evaluation of the hypertensive individual and may obviate the need for expensive and unnecessary evaluations. Discontinuation of the offending agent will usually achieve adequate blood pressure control. When use of a chemical agent which increases blood pressure is mandatory, anti-hypertensive therapy may facilitate continued use of this agent.

We summarize the therapeutic agents or chemical substances that elevate blood pressure and their mechanisms of action.

1. Introduction

Most patients with high blood pressure have essential hypertension or well-known forms of secondary hypertension. Drug and chemical substances are frequently overlooked as a secondary cause of hypertension. Therefore, a comprehensive history including use of medications, over the counter agents and illegal substances should be elicited in every hypertensive individual. Identification of these substances may obviate the need for unnecessary, costly, and potentially dangerous evaluations, treatments, or both (Elliott, 2006; Grossman and Messerli, 1995; Rossi et al., 2011).

We recently reviewed the therapeutic agents and chemical substances that may elevate blood pressure (Grossman and Messerli, 2012). This manuscript updates our previous review on drug induced hypertension (Table 1). For some agents that are more commonly used we will review the available data.

2. Anti neoplastic agents

Several alkylating agents can increase blood pressure. In one serious 15 of 18 patients treated with multiple alkylating agents following autologous bone marrow transplantation developed hypertension (Grossman and Messerli, 2008). Hypertensive reactions associated with paclitaxel treatment have been reported (Solimando et al., 1996). Cis-diamminedichloroplatinium (CDDP) is an organic platinum compound with an antineoplastic effect. It has been demonstrated in four of five patients that intraarterial administration of CDDP produces sustained systemic hypertension. This complication has not been observed in patients receiving the drug by the intravenous route (Grossman and Messerli, 2008).

In the last years vascular endothelial growth factors (VEGF)

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inhibitors are being increasingly used for the treatment of various malignancies. This group of agents includes mainly monoclonal antibodies such as bevacizumab (Avastin), or orally-available small molecules that inhibit the tyrosine kinases stimulated by VEGF such as lapatinib (Tykerb), sunitinib (Sutent), sorafenib (Nexavar), axitinib, and pazopanib. These new drugs are most frequently involved with the development of hypertension (Milan et al., 2014). The development of hypertension is important in patients with malignancies because chemotherapy reduces cancer-related morbidity and mortality and patients are expected to live longer. Therefore, the impact of poorly controlled hypertension on cardiovascular morbidity and mortality may become a major issue. Bevacizumab (Avastin) is used to treat metastatic cancers of various origins. In clinical trials the development of moderate hypertension was more prevalent in patients treated with bevacizumab. The incidence of severe hypertension(blood pressure > 200/100 mmHg) was > 3- to 5-fold higher in the bevacizumab groups compared with placebo.(Hurwitz et al., 2004; Kozloff et al., 2009; Shih and Lindley, 2006) In the initial studies on bevacizumab, hypertension was reported in up to 32% of patients, but only 1% had life threatening hypertensive crisis (Izzedine et al., 2009). In a recent report describing the real-world association between baseline clinical characteristics, blood pressure response, and survival in patients prescribed anti-VEGF therapies., treatment-induced hypertensive response was identified in 49.7% of patients (Hamnvik et al., 2015). The absolute observed mean increase in blood pressure was 21 mmHg (systolic)/15 mmHg (diastolic), both in patients with and without preexisting hypertension. The incidence of hypertension was dose related and preexisting hypertension, old age (≥ 60 years), and overweight (≥ 25 kg/m^2) were risk factors for anti-VEGF therapy-induced blood pressure elevation (Hamnvik et al., 2015). In addition, it seems that blood pressure elevation associated with bevacizumab predicts a favorable response to treatment (Hamnvik et al., 2015).

Intravitreal bevacizumab injection is safe in terms of BP in both hypertensive and normotensive patients (Lee et al., 2009), however in one study 27 out of 768 patients (3.5%) reported a new episode of hypertension during intraocular injections of bevacizumab (Sheybani et al., 2009).

Sorafenib that is approved for advanced renal cell carcinoma and hepatocellular carcinoma can also increase blood pressure. In the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), treatment-related hypertension was reported in17% of the patients. Stage 2 hypertension was reported in 4% of the sorafenib treated patients compared to less than 1% in the controls (Escudier et al., 2007). Unlike the findings of the TARGET trial in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) patients with advanced hepatocellular carcinoma who were treated with sorafenib 400 mg BID did not develop more hypertension than the control group (Llovet et al., 2008). In a recent meta-analysis the relative risk for the development of hypertension was increased (relative risk [RR]: 2.93; 95% CI: 1.52–5.66) with the use of sorafenib compared with placebo and was independent on the tumor type and treatment regimen (Abdel-Rahman and Fouad, 2014a). Maitland et al. showed, by using 24 h ambulatory blood pressure monitoring, that sorafenib 400 mg BID increased systolic blood pressure by 8.2 mmHg and diastolic blood pressure by 6.5 mmHg within 24 h of treatment (Maitland et al., 2009).

Sunitinib (Sutent), an oral receptor tyrosine kinase inhibitor, has also been associated with hypertension (Zhu et al., 2009).

Hypertension should be considered as a class effect of all anti-angiogenic therapies and it seems that the risk of hypertension is similar with all agents(Abdel-Rahman and Fouad, 2014b; Wu et al., 2008). The use of VEGF signaling inhibitors is usually associated with mild blood pressure increase. However, it may be associated with severe hypertension, and Reversible Posterior Leukoencephalopathy Syndrome-a significant event likely secondary to hypertension (Levy et al., 2009). About 1% of all patients on anti-angiogenic therapy develop a hypertensive emergency.

The mechanism of elevated blood pressure in patients treated with anti-angiogenic agents is likely to be multifactorial and may include a decrease in nitric oxide (NO) production, loss of anti oxidative effect, and activation of the endothelin-1 system(Gonzalez-Pacheco et al., 2006; Hood et al., 1998; Kappers et al., 2010; Small et al., 2014). Recently, Thijs et al. showed that bevacizumab may increase peripheral resistance and blood pressure by reducing endothelium-mediated vasodilation (Thijs et al., 2013).

Several studies have suggested that hypertension may predict a beneficial response to antiangiogenics (Bono et al., 2009). Anti-VEGF therapy-associated hypertension is often transient and typically resolves with discontinuation of the provoking agent. Elevated blood pressure is usually easily controlled and the immediate risk of hypertensive target organ diseases is low in most patients. However, one should keep in mind that hypertensive crisis may occur, and therefore a close monitoring of blood pressure and early initiation of anti-hypertensive agents when necessary is recommended.

In an animal model Lankhorst et al. showed that the dual endothelin receptor antagonist-macitentan and the calcium channel blocker amlodipine can prevent sunitinib induced hypertension (Lankhorst et al., 2014).

Renin angiotensin system inhibitors, diuretics, beta blockers and calcium antagonists may be used to lower blood pressure. The nondihydropyridine calcium antagonists such as verapamil and diltiazem, are CYP3A4 inhibitors and nifedipine a dihydropyridine calcium antagonist has been shown to induce VEGF secretion, and therefore should be used with caution in combination with oral angiogenic inhibitors (Izzedine et al., 2009). Nitrates may increase the production of endogenous NO thereby facilitating blood pressure control (Dirix LYMaes and Sweldens, 2007). A favorable blood pressure response to sublingual test dose of 5 mg isosorbide dinitrate has been used to predict response to long acting nitrates (Dirix LYMaes and Sweldens, 2007).

3. Nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics

NSAIDs can produce a clinically significant increment in mean blood pressure of 5 mmHg (Johnson, 1997). While the mechanism involved in blood pressure increase remain speculative, salt and water retention coupled with increased total peripheral vascular resistance, via increased renal endothelin-1 synthesis may be the culprits (Johnson, 1997). NSAIDs diminish the effectiveness of some antihypertensive agents such as diuretics, beta-blockers and ACE inhibitors, but do not interfere with the action of calcium antagonists and central acting drugs (Krum et al., 2009; Morgan and Anderson, 2003; Singh et al., 2014).

NSAIDs vary considerably in their effect on BP. Armstrong and Malone found among the various NSAIDs, that indomethacin, naproxen, and piroxicam were associated with the greatest increase in blood pressure (Armstrong and Malone, 2003). Among the selective NSAIDs rofecoxib was more likely than celecoxib to raise systolic blood pressure (Armstrong and Malone, 2003). Two meta-analyses showed that selective COX-2 inhibitors increase blood pressure more than the nonselective agents (Aw et al., 2005; Chan et al., 2009). Unlike these findings Wang et al. (2007) showed that there were similar hazard rates of incident hypertension with celecoxib and nonselective NSAIDs users. Several studies showed that rofecoxib (which is now off the market) increased blood pressure more than celecoxib (Aw et al., 2005; Sowers et al., 2005).