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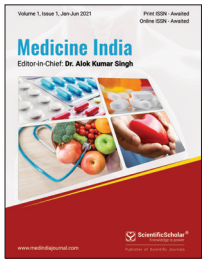

Case Series

Apparent treatment resistant hypertension. The drug could be culprit

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ABSTRACT

Treatment of hypertension to goal should be the goal if its morbi-mortality consequences are to be curtailed. Notwithstanding, this ideal however, sub-optimal control plagues clinical practice largely due to non-adherence, adverse side-effects, and outright intolerance. When there is apparent treatment failure, the tendency is to consider these. If adjudged to be resistant or refractory to treatment, device therapy is contemplated notwithstanding cost implications and its invasive nature. Little attention is paid to the phenomenon of paradoxical hypertension, wherein in the presence of certain antihypertensives, blood pressure actually rises rather than falls. How much of this that occurs in clinical practice is not exactly known, but continuing to add new drug classes or increase doses in such situations will increase cost and possibility of side effects without optimal control. Target organ damages would persist with worse outcomes. The evolving area of pharmacogenomics is showing that for some genetic reasons, certain individuals would respond to certain drugs and not others. This may manifest in the occasional instances of paradoxical rise in blood pressure with the introduction of certain blood pressure drug classes. The authors encountered a few such cases and considered them of interest to other clinicians who manage difficult to treat hypertension. When hypertension treatment is sub-optimal especially rising with new drug introduction, it may be worth switching drugs just in case a paradoxical response to a drug class is responsible for non-response.

Keywords: Hypertension, Treatment, Drugs, Resistance, Induction

INTRODUCTION

Treatment of hypertension has been plagued with suboptimal control. It is known that only about 21% of people identified as hypertensive and on treatment have their blood pressure controlled.[1] This leaves the bulk of the afflicted at risk of target organ damage, morbidity, and mortality. Given the fact that hypertension is polygenic in inheritance, its treatment is bound to be broad based, with the individual's nature and nurture determining whether any particular drug will work in any given situation.[2] The prevalence of treatment resistant hypertension in medical literature varies depending on sample size and population cohort studied. In a specialized hypertension clinic run by the author, given that most of the hypertensives were referred for "difficult to control" hypertension the prevalence rate reported in a practice audit was 54.9%.[3]

Encountering the report on pressor response to antihypertensive drugs in clinical practice,[4] got the author curious and on the lookout for such cases among the hypertensives, in whom control was difficult at some points with some drug types. Three such cases encountered are hereby reported for the benefit of clinicians involved in managing hypertension generally and apparent treatment resistant hypertension in particular. Drug change is usually the panacea.

CASE SERIES

1. Case 1 was an 80-year-old female whose blood pressure remained above goal at 140/94 mmHg despite triple therapy (Losartan 50 mg daily, hydrochlorothiazide 12.5 mg daily, and spironolactone 25 mg twice daily). Because the pulse rate at that visit was on the high side of normal, a beta-blocker carvedilol was added to her regimen at 2.5 mg daily. On review at her next visit and despite reported adherence, the blood pressure had risen to 157/102 mmHg. She was given some more time on this regimen and blood pressure still stood at 156/102 mmHg. At this point, the carvedilol was increased to 5 mg and the others unchanged. When she came next it was 150/96 mmHg, but she was complaining about recent onset shortness of breath. The beta-blocker carvedilol was dropped together with hydrochlorothiazide. She returned for her next appointment a few weeks later and the blood pressure was now 135/74 mmHg.
2. Case 2 was a 57-year-old female who had hypertension, diabetes mellitus, and dyslipidemia. She was on vidagliptin/metformin combination 50/1000 twice daily, glibenclamide 5 mg daily, pioglitazone 30 mg daily, simvastatin 10 mg nocte, losartan 50 mg daily, and amlodipine 10 mg daily. Blood pressure at this visit was 170/100 mmHg. When on review after 2 weeks and blood pressure remained above goal, prazosin/hydrochlorothiazide 0.5/12.5 mg combination was added. Despite this, blood pressure rose to 180/100 mmHg. She was counseled on lifestyle and adherence and asked to persevere. She could not refill her prescription as the drug disappeared from the Nigerian market. When she came on her due appointment, the blood pressure reading had dropped to 130/80 mmHg.
3. Case 3 was also female, and 43 years old. When she was first seen, her blood pressure was 144/100 mmHg on amiloride/hydrochlorothiazide 5/50 mg combination. Valsartan 80 mg was added to her treatment. Two weeks later, the blood pressure had risen to 167/100 mmHg. She was counseled on lifestyle modification and adherence positively re-inforced, then given a 4 week appointment. She returned with a blood pressure of 188/108 mmHg. At this point, Valsartan was dropped and Nebivolo l 5 mg daily was added. On her next follow-up visit, the blood pressure had dropped to 135/88 mmHg.

COMMENTS

Adherence to treatment granted, patients may not attain blood pressure control for various reasons. One is drug intolerance. Some individuals exhibit intolerance to antihypertensives in the presence of which blood pressure control becomes sub-optimal.[5] Intolerance is upsetting to homeostasis and constitutes an internal stress, in the presence of which blood pressure remains elevated. In some instances, adverse effects, which are more common, predictable, and deriving from the drug's pharmacological action, could be the reason for sub-optimal control. Some adverse effects such as body pains, headache, palpitations, and insomnia could upset the patient physically and counter the blood pressure lowering effect of the drug. Side effects like sexual dysfunction are more likely to lead to non-adherence.

In a few cases, neither adverse effect nor intolerance may exist but rather a paradoxical rise in blood pressure occurs with drug intake. One had encountered in the past a middle aged man whose blood pressure would go up with several antihypertensives taken except that he was prescribed amiloride/hydrochlorothiazide 5/50 mg combination. Such situations may result from pressor responses to the culprit antihypertensive drug types like the cases reported by Aldermann *et al*.[4] of beta-blockers and angiotensin converting enzyme inhibitors in lower renin patients. This phenomenon is awakening interest in pharmacogenomics in the treatment of hypertension especially when patients present with "difficult to control" hypertension.[6]

Uncontrolled hypertension is said to be partly due to drug response variability as a result of genetic polymorphism.[2] By the alteration of metabolism of drugs by some genetic polymorphisms, some antihypertensive drugs are rendered ineffective in lowering blood pressure.[7] Furthermore, gut microbiota has a role, as in the presence of certain gut commensals blood pressure lowering effect of some class of antihypertensives is compromised.[8]

In the cases reported, the situation was slightly different. It was not blood pressure unresponsive with a drop but actually rising with addition of certain antihypertensive drug classes. For Case 1, blood pressure rose further with introduction of a beta blocker normalizing only when the beta-blocker was removed. For Case 2, blood pressure rose with the addition of an alpha-blocker/thiazide diuretic combination. Fortuitously, their blood pressure normalized when she could no longer access the drug. For Case 3, the introduction of an angiotensin receptor blocker got the blood pressure rising, a fall being recorded only after it was replaced. Pressor effect of antihypertensive drugs has been reported for beta-blockers[9] and blockers of the renin angiotensin aldosterone system.[4] For beta-blockers, it is put to the beta blockade leaving the alpha receptors available for vasoconstriction and rise in blood pressure.[4] In the case of blockers of the renin angiotensin aldosterone system, the explanation is drug induced increase in renal renin secretion similar to that induced by sodium deprivation especially in low renin patients.[4]

Although no case of paradoxical rise in blood pressure was encountered in literature with alpha-blockers, it is being

speculated that if for some genetic reasons, there is extreme vasodilatation with the drug, the sharp drop in blood pressure could evoke counter regulatory renal mechanisms that could cause a rise in blood pressure. Patients did not undergo continuous blood pressure monitoring. As such it is not possible to tell at what point the blood pressure rose except that after a few weeks when patient came for review, the blood pressure was noted to have risen higher. Non-availability of the drug resulting in normalization proves by default that it was the culprit.

An interesting observation here is that all the cases were female. This is not entirely a new phenomenon. Women are known to report more drug related side effects than men to antihypertensive drugs[10] as well as multi-drug intolerance.[5]

CONCLUSION

Until pharmacogenetics can be applied in selected cases to "difficult to treat" hypertension, it may be a fruitful exercise to juggle drugs especially those whose introduction is followed by a paradoxical rise in blood pressure.

Disclosure

The author has no disclosure to make with regard to this manuscript.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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