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Multidrug intolerance in the treatment of hypertension: result from an audit of a specialized hypertension service

Basil N. Okeahialam

Abstract

Background: Hypertension as a cardiovascular disease risk factor continues to take a heavy toll on the population despite efforts with containment. Poor control, even among those on treatment, is part of the challenge and results from patient, physician and health system factors. When the problem resides at patient level, adherence is largely responsible. An entity defined as multidrug intolerance (MDI) is hardly considered. A situation when a patient is willing to adhere but is compelled otherwise could frustrate both patient and physician. Encountering a few such cases prompted the author to audit his specialized hypertension service in order to evaluate the burden of MDI and its associations.

Methods: Between 7 May and 30 July 2016 (to cover a 12-week cycle which ensured all attendees were captured), all patients attending follow up for blood pressure control had their records evaluated for intolerance to three or more different classes of anti-hypertensives, which defines MDI. Their ages, sex, control state and co-morbidities were extracted from the records.

Results: A total of 489 patients with hypertension were seen over the period; 271 (55.4%) of whom were women and 248 (50.7%) were uncontrolled. Overall 15 (3.1%) satisfied the definition of MDI; 10 women and 5 men. All the men with MDI were uncontrolled while 7 out of the 10 women were uncontrolled; with two having premenstrual syndrome as co-morbidity. A total of four patients (three men, one woman) had history suggesting allergy and two (one man, one woman) were on treatment for anxio-depressive illness.

Conclusion: MDI does occur in sub-Sahara African patients with hypertension and should be considered before describing hypertension as resistant or considering alternative treatments including device therapy. Staggering doses or trying different formulations could be of benefit.

Keywords: drug, hypertension, intolerance, multiple, Nigeria, poor control

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Correspondence to:
Basil N. Okeahialam,
Cardiology Sub-Unit 1, Department of Medicine, Jos University Teaching Hospital, PMB 2076, Jos, Plateau, 930001, Nigeria
basokeam@yahoo.com

Introduction

Adverse drug reactions (ADRs) negatively affect drug adherence[1] and in the treatment of hypertension result in sub-optimal blood pressure control. This takes a heavy toll on patients with regard to morbidity and mortality. When a patient is intolerant of three or more drugs with no clear immunological mechanism, a clinical entity called multidrug intolerance (MDI) is said to exist.[2] According to some workers,[3] it occurs almost exclusively in patients of white European ethnicity. One encounters in practice in Jos, Nigeria, patients who are intolerant of anti-hypertensives at initiation or at some point down the line of treatment. This variability in time-to-symptom has been previously observed. When early, pre-existing cross reactive memory CD8 T-cells are pathogenic while immune-mediated ADRs of delayed onset results from activation of *de novo* T-cells.[4] This makes control impossible, frustrating the physician and leaving the patient at risk of complications, with huge economic and psychosocial consequences. At times life is lost.

This entity which patients describe poorly or with difficulty stands in the way of treatment as control

is poor[3] and patients resist re-introduction of drugs for treatment. This makes them willing converts to phytomedicine and nutraceuticals in the erroneous belief that as 'natural products', they are like food and devoid of untoward effects. Encountering a few among local patients in this sub-Sahara African facility, against the back drop that it has not been reported in Blacks despite their association with resistant hypertension,[5] one was encouraged to scrutinize the hypertension database of this specialized hypertension service. This was with a view to assessing the quantum of the problem, and to be able to plan containment strategies. No series of this entity has been reported in our sub-region to the best of the author's knowledge.

Methodology

The author runs a purely outpatient-based specialized hypertension service in Jos, Nigeria where patients come on their own volition or are referred from about 10 out of the 36 states of Nigeria. Occasionally they come from far-flung states on the advice of their relations resident in Jos. The reasons for referral vary but are mostly for hypertension associated with target organ involvement, co-morbidities and difficulties to control. Effectively, patients come from all cultural backgrounds and cut across sex and socioeconomic strata in Nigeria, the most populous Black nation in the world.

Patients are seen solely by the author and are given appointments ranging from 2–12 weeks. Over 3 months (May–July 2016) to cover a 12-week cycle which ensured all attendees were captured, all patients with hypertension consulting the author had their records evaluated for intolerance to three or more different classes of anti-hypertensives. This was made easy because as a matter of practice, any reported drug intolerance is usually documented on the case note to avoid patients being prescribed such drugs subsequently. Drugs prescribed depended on patients' cardiovascular disease profile. The consent for use of data of those with documented evidence of intolerance to three or more anti-hypertensives was sought and given in all instances. Their ages, sex, control status and co-morbidities were extracted from the records and entered on a data collection sheet. No patient was recorded more than once. Data were anonymized to avoid breach of confidentiality, obviating the need for Institutional Board Review. Only frequencies and percentages are presented.

Results

A total of 489 patients with hypertension were seen, 271 (55.4%) of whom were women. About half 248/489 were uncontrolled. Overall, 15 out of the 489 (3.1%) consisting of 10 women and five men, satisfied the definition of MDI. Their ages ranged from 38–71 years of age with most of them being in their 7th decade of life. All the 5 men in this sub-group were uncontrolled while 7 out of the 10 women were uncontrolled. Overall, two of the women suffered from premenstrual syndrome. A total of 8 out of the 15 (2 men, 6 women) had a history suggestive of allergy; and two (1 man, 1 woman) were on treatment for anxio-depressive illness. Most drug classes were represented and patients reported palpitations, dizziness, tinnitus, insomnia, headache, body aches and being restless as symptoms of intolerance, which were of such severity to interfere with daily routine and prompt discontinuation before reporting to author. In some cases, the intolerance was reported with one brand only of a drug and not the others, or they would initially tolerate a drug but show intolerance later and vice versa. Table 1 shows details of drugs the patients were intolerant of with co-morbidities and current regimen.

Discussion

There are individual and group variations in drug response in different disease entities.[6] With hypertension, inter-patient variability in drug response could be huge, and reasons for varying response to a particular drug and cardiovascular outcomes are still blurred.[7] As a result, a more person-centered approach to treatment of hypertension would be beneficial. This nonuniformity in response led some workers to wade into a new frontier of 'personalized medicine', which for hypertension, seeks to avert patient-specific risk factors for ADRs.[8] Though most ADRs to antihypertensives do not threaten life directly, they do so indirectly by contributing to nonadherence and adverse outcomes with heavy economic burden.[9] Generally, ADRs are said to be a great burden to patients and health systems alike, with the majority being predictable (Type A/on-target) and about 20% which are not readily anticipated (Type B/off-target).[4]

Almost all drug classes were involved and prominent symptoms of intolerance prompting discontinuation included palpitations, dizziness, tinnitus, insomnia and body aches among others. More women were affected in this series.

Table 1. Drugs causing intolerance with description of reactions in study population.

S/No	Sex	Age	HBP drugs	Reaction	Other drugs	Remarks[b]
1	F	58 years	Atenolol	'Bad'[a]	Cataflam	Moduretic daily
			Nifedipine	Backache[c]	C/Col	Carvedilol 3.125 mg daily
			Moduretic	Cough[c]		(No co-morbidity)
2	F	64 years	Norvasc	Headache	Maldox	Miniplus daily
			Diovan	'Terrible'[a]		Norvasc 10 mg daily
			Amlovas	Very weak[c]		(Co-morbid diabetes)
			Zestoretic	Dizzy		
			Telmisartan	Body pain[c]		
			Inderal	Plantar pain[c]		
			Tritazide	Body pain[c]		
			Arbitel – H	Body itching[c]		
3	M	66 years	Miniplus	Tinnitus[c]	Ciproflox	Nebilong 5 mg daily
			Rosart	Headache[c]	Erythromycin	(Co-morbid depression)
			Atenolol	Tight chest		
			Exforge HCT	Body pain[c]		
			Norvasc	'Bad'[a]		
			Moduretic	Body pain[c]		
			Nebilong-H	Tinnitus[c]		
4	F	34 years	Thiapril	Tinnitus[c]	Depo-Provera	Ramitace 2.5 mg in 3 days
			Lofral	Epigastric pain[c]	Fansidar	(Co-morbid PMS)
			Ramitace	Dizziness	Zaditen	
			Miniplus	Palpitations[c]	Amiodarone	
			Tritace	Chest pain[c]	Tryptizol	
5	F	63 years	Atenolol	Palpitations[c]	Amoxyl	Asomex 2.5 mg 5 days/weeks
			Losartan	Heartburn[c]	Rosuvastatin	Aldactone 25 mg 2 days/weeks
			Thiapril	Cough		(Co-morbid depression)
			Asomex	Head ache		
			Miniplus	Insomnia[c]		
			Tenoric	Head ache[c]		
6	F	54 years	Sinepress	Flushing	Cognitol	Moduretic daily
			Atenolol	'Bad'[a]	Coenzyme Q10	Atenolol 25 mg in 3 days
			Moduretic	Palpitations[c]	Eve	(Co-morbid PMS)
7	M	62 years	Miniplus	'Bad'[a]	Crestor	Plendil 5 mg daily
			Moduretic	Chest pain[c]	Aldactone 12.5 mg daily	
			Co-Diovan	Body pain[c]	(Co-morbid Met Syn)	
8	F	66 years	Atenolol	Palpitations[c]	Oruvail	Hydrex 50 mg daily
			Nifedipine	Insomnia[c]		(Co-morbid Rh. Dx)

(Continued)

Table 1. (Continued)

S/No	Sex	Age	HBP drugs	Reaction	Other drugs	Remarks[b]
			Junolol	Palpitations[c]		
			Cascor	Insomnia[c]		
			Hydrex	Palpitations[c]		
9	F	68 years	Rosart	Body pain[c]	Nil	Tenoric 25 mg alt day
			Miniplus	Tinnitus[c]		S/amlodipine 2.5 mg daily
			Carvedilol	Catarrh[c]		
			Atenolol	Headache[c]		
10	F	65 years	Cladipine	Headache	Nil	No drug
			Tenoretic	Dry skin	Nil	
			Thiapril	Carpal spasms[c]		
11	M	38 years	Cardvedilol	Headache[c]	Nil	Miniplus daily
			Acefex	Headache		
			Arbitel H	Headache[c]		
12	M	63 years	Miniplus	Heaviness[c]	Nil	Hyporetic daily
			Amlodipine	Heaviness[c]		Aldactone 25 mg daily
			Hyporetic	Head ache[c]		Lasix 40 mg daily
			Twynstar	'Bad'[a]		(Co-morbid Stroke)
13	F	54 years	Lisinopril	Headache[c]	Nil	Nebilong 2.5 mg weekly
			Moduretic	'Bad'[a]		
			Aldomet	Lethargy		
			Amlodipine	'Bad'[a]		
			Nebilong-H	Headache[c]		
14	F	56 years	Aldactone	Giddiness[c]	Dolobid	Aldactone 25 mg bid
			Thiapril	Weight gain[c]	Perfloxacin	(Co-morbid MetSyn)
			Asomex	Body pain[c]		
			Cardrex	Ankle swelling		
			Lisofil	Wheezing		
			Carvedilol	'Bad'[a]		
			Diovan	Headache[c]		
15	M	71 years	Diovan	Giddiness	Aloe vera	Cilzec 40 mg in 3 days
			Co-diovan	Body rash[c]	Voltaren	(Co-morbid Met Syn)
			Moduretic	Joint pains	Cashew nuts	
			Aldomet	Body rash[c]		
			Asomex	Palpitation		
			Losium	Body itching[c]		
			Brinerdin	Body rash		
			Arbitel H	'Bad'[a]		

[a]'Bad' and 'Terrible' were terms used by patients to describe reactions that they could not clearly describe.
[b]Drugs under remarks column are current regimen.
[c]Indicates reactions not readily anticipated from pharmacology and considered Type B or off-target. C/Col, chloramphenicol; F, female; M, male; Met Syn, metabolic syndrome; Nebilong-H, nebivolol + hydrochlorothiazide; PMS, premenstrual syndrome; Rh. Dx, rheumatoid disease.

Sex representation has varied in different series, though on balance more women are reportedly affected.[3] Physiological differences impacting on pharmacokinetics and pharmacodynamics across sexes are considered plausible.[10] Patients with a background of allergy are also said to be prone, as some of them would also have ADRs to other drug classes.[11] Overall, 8 eight of them also reacted to either or both of antibiotics or non-steroidal anti-inflammatory drugs. (See Table 1). For these, altered mast cell degranulation may be the underlying mechanism.[12] An imbalance of the immune system manifesting excess activation of effector T-cells and inadequately low function of T-Reg cells has been reported in some cases.[13] In this series 8/15 gave histories suggesting allergy disease and may actually have what is called 'multiple drug allergy syndrome'. The link with anxio-depressive illness has also been made.[14] This is because of their predisposition to nocebo effect[15] and some nonpharmacologically expected as well as nonidiopathic ADRs which are exaggerated in severity.[16] Overall, 2 of the 15 patients meeting the criteria for diagnosis of MDI in this series were already on treatment for anxio-depressive disorders.

The 3.1% prevalence of MDI in this series is slightly higher than the 2.1% in the United States (US) population.[17] It is understandable since this series focused on patients with hypertension in a specialized hypertension clinic while the US data were population-wide. Some MDI reactions may arise from nonspecific histamine release. Histamine in the human circulation evokes the release of adrenaline from the adrenal glands. This would increase the rate and force of cardiac contraction[11] resulting in instances of palpitation, headache, tinnitus, increased alertness and insomnia, anxiety and panic attacks. Reactions to drug classes in one formulation as opposed to another may be due to difference in excipients used by different manufacturers or differences in physicochemical properties of solid dose formulations.[3] All considered, the fact that 12/15 patients satisfying the diagnosis of MDI had their blood pressures uncontrolled shows how much this can cause sub-optimal control and should worry clinicians caring for patients with hypertension. For these patients, it may be helpful to consider reducing total cardiovascular disease risk profile rather than pushing blood pressure reduction to an arbitrary cutoff point with attendant risk of drug reaction and its consequences. In such cases, a higher blood pressure level may be accepted as 'satisfactory goal' provided other cardiovascular disease risk factors which increase morbidity are well controlled.

In conclusion, MDI does occur in Nigerian patients with hypertension. When blood pressure control is poor and drug adherence is suspect, the possibility of MDI should be explored among other issues. Such patients should be offered staggered doses of solid formulations, liquefied or topical formulations before considering device-based therapy. Staggered doses of solid formulations seem to work here in preventing ADRs (See Table 1) where drugs are given on alternate days, every third day and once a week. Liquefied and topical formulations were not readily available and hence not administered.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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